CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-073/s-010

Trade Name: Actos

Generic Name: Pioglitazone Hydrochloride

Sponsor: Takeda Pharmaceuticals North America, Inc.

Approval Date: July 12, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-073/s-010

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-073/ S-010

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-073/S-010

Takeda Pharmaceuticals North America, Inc.
Attention: Janet L. Haskins
Regulatory Affairs Supervisor
475 Half Day Road, Suite 500
Lincolnshire, IL 6069

Dear Ms. Haskins:

Please refer to your supplemental new drug application dated March 2, 2001, received March 5, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Actos (pioglitazone) Tablets.

We acknowledge receipt of your submissions dated January 11 and 22, and July 12, 2002(facsimile). Your submission of January 11, 2002 constituted a complete response to our January 4, 2002 action letter.

This supplemental new drug application provides for changes to the PRECAUTIONS section, Drug Interactions subsection. The pharmacokinetics of concomitant use of pioglitazone with the following compounds was added: fexofenadine, ranitidine, and nifedipine ER. The balance of the subsection was reworded to reduce redundancy.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the attached draft labeling.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 21-073/S-010." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Jena Weber, Regulatory Project Manager, at (301) 827-6422.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Orloff
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-073/ S-010

APPROVABLE LETTER

NDA 21-073/S-010

Takeda Pharmaceuticals North America, Inc.
Attention: Janet L. Haskins
Regulatory Affairs Supervisor
475 Half Day Road, Suite 500
Lincolnshire, IL 60069

Dear Ms. Haskins:

Please refer to your supplemental new drug application dated March 2, 2001, received March 5, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Actos® (pioglitazone HCl) Tablets, 15 mg, 30 mg and 45 mg.

This supplemental new drug application proposes revisions to the **PRECAUTIONS** section, **Drug Interactions** subsection of the package insert.

We have completed the review of this application, and it is **approvable**. Before this application may be approved, however, it will be necessary for you to submit revised draft labeling. All of the following drug interaction studies should be ~~[illegible]~~ **CLINICAL PHARMACOLOGY** section, **Drug-Drug Interactions** subsection, following **Ethnicity** after the **Special Populations** subsection. The sections describing Oral Contraceptives and Cytochrome P450 should remain under the **PRECAUTIONS** section, **Drug Interactions** subsection.

CLINICAL PHARMACOLOGY section, **Drug-Drug Interactions** subsection, following **Ethnicity** under **Special Populations** subsection should read:

The following drugs were studied in healthy volunteers with a co-administration of ACTOS 45 mg once daily. Listed below are the results:

Fexofenadine HCl: Co-administration of ACTOS for 7 days with 60 mg fexofenadine administered orally twice daily ~~[illegible]~~ fexofenadine pharmacokinetics.

Glipizide: Co-administration of ACTOS and 5 mg glipizide administered orally once daily for 7 days did not alter the steady-state pharmacokinetics of glipizide.

Digoxin: Co-administration of ACTOS with 0.25 mg digoxin administered orally once daily for 7 days did not alter the steady-state pharmacokinetics of digoxin.

Warfarin: Co-administration of ACTOS for 7 days with warfarin did not alter the steady-state pharmacokinetics of warfarin. ACTOS has no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy.

Metformin: Co-administration of a single dose of metformin (1000 mg) and ACTOS after 7 days of ACTOS did not alter the pharmacokinetics of the single dose of metformin.

Ranitidine HCl: Co-administration of ACTOS for 7 days with ranitidine administered orally twice daily for either 4 or 7 days resulted in

Nifedipine ER: Co-administration of ACTOS for 7 days with 30 mg nifedipine ER administered orally once daily for 4 days

Ketoconazole: Co-administration ACTOS and ketoconazole (200 mg) resulted in

Midazolam: Administration of ACTOS for 15 days followed by a single 7.5 mg dose of midazolam syrup resulted in a 26% reduction in midazolam C_{max} and AUC.

Oral Contraceptives: See **PRECAUTIONS**

Cytochrome P450: See **PRECAUTIONS**

PRECAUTIONS section, **Drug Interactions** subsection should read:

Oral Contraceptives: Administration of another thiazolidinedione with an oral contraceptive containing ethinyl estradiol and norethindrone reduced the plasma concentrations of both hormones by approximately 30%, which could result in loss of contraception. The pharmacokinetics of co-administration of ACTOS and oral contraceptives have not been evaluated in patients receiving ACTOS and an oral contraceptive. Therefore, additional caution regarding contraception should be exercised in patients receiving ACTOS and an oral contraceptive.

The cytochrome P450 isoform CYP3A4 is partially responsible for the metabolism of pioglitazone. Specific formal pharmacokinetic interaction studies have not been conducted with ACTOS and other drugs metabolized by this enzyme such as: erythromycin, astemizole, cisapride, corticosteroids, cyclosporine, HMG-CoA reductase inhibitors, tacrolimus, triazolam, and trimetrexate, as well as inhibitory drugs such as ketoconazole and itraconazole. In vitro, ketoconazole appears to significantly inhibit the metabolism of pioglitazone (see CLINICAL PHARMACOLOGY, Metabolism).

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If you elect to submit final printed labeling (FPL), please submit the copies electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL, ten of which should be individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at (301) 827-6422.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

David Orloff
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-073 / S-010

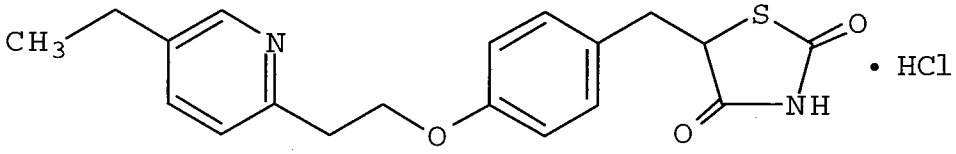
APPROVED LABELING

ACTOS®
(pioglitazone hydrochloride) Tablets

DESCRIPTION

ACTOS (pioglitazone hydrochloride) is an oral antidiabetic agent that acts primarily by decreasing insulin resistance. ACTOS is used in the management of type 2 diabetes mellitus (also known as non-insulin-dependent diabetes mellitus [NIDDM] or adult-onset diabetes). Pharmacological studies indicate that ACTOS improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. ACTOS improves glycemic control while reducing circulating insulin levels.

Pioglitazone [(±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-] thiazolidinedione monohydrochloride belongs to a different chemical class and has a different pharmacological action than the sulfonylureas, metformin, or the α-glucosidase inhibitors. The molecule contains one asymmetric carbon, and the compound is synthesized and used as the racemic mixture. The two enantiomers of pioglitazone inter-convert in vivo. No differences were found in the pharmacologic activity between the two enantiomers. The structural formula is as shown:



Pioglitazone hydrochloride is an odorless white crystalline powder that has a molecular formula of $C_{19}H_{20}N_2O_3S$•HCl and a molecular weight of 392.90 daltons. It is soluble in N,N-dimethylformamide, slightly soluble in anhydrous ethanol, very slightly soluble in acetone and acetonitrile, practically insoluble in water, and insoluble in ether.

ACTOS is available as a tablet for oral administration containing 15 mg, 30 mg, or 45 mg of pioglitazone (as the base) formulated with the following excipients: lactose monohydrate NF, hydroxypropylcellulose NF, carboxymethylcellulose calcium NF, and magnesium stearate NF.

CLINICAL PHARMACOLOGY

Mechanism of Action

ACTOS is a thiazolidinedione antidiabetic agent that depends on the presence of insulin for its mechanism of action. ACTOS decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output. Unlike sulfonylureas, pioglitazone is not an insulin secretagogue. Pioglitazone is a potent and highly selective agonist for peroxisome proliferator-activated receptor-gamma (PPARγ). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism.

In animal models of diabetes, pioglitazone reduces the hyperglycemia, hyperinsulinemia, and hypertriglyceridemia characteristic of insulin-resistant states such as type 2 diabetes. The metabolic changes produced by pioglitazone result in increased

responsiveness of insulin-dependent tissues and are observed in numerous animal models of insulin resistance.

Since pioglitazone enhances the effects of circulating insulin (by decreasing insulin resistance), it does not lower blood glucose in animal models that lack endogenous insulin.

Pharmacokinetics and Drug Metabolism

Serum concentrations of total pioglitazone (pioglitazone plus active metabolites) remain elevated 24 hours after once daily dosing. Steady-state serum concentrations of both pioglitazone and total pioglitazone are achieved within 7 days. At steady-state, two of the pharmacologically active metabolites of pioglitazone, Metabolites III (M-III) and IV (M-IV), reach serum concentrations equal to or greater than pioglitazone. In both healthy volunteers and in patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the peak total pioglitazone serum concentrations and 20% to 25% of the total area under the serum concentration-time curve (AUC).

Maximum serum concentration (C_{max}), AUC, and trough serum concentrations (C_{min}) for both pioglitazone and total pioglitazone increase proportionally at doses of 15 mg and 30 mg per day. There is a slightly less than proportional increase for pioglitazone and total pioglitazone at a dose of 60 mg per day.

Absorption: Following oral administration, in the fasting state, pioglitazone is first measurable in serum within 30 minutes, with peak concentrations observed within 2 hours. Food slightly delays the time to peak serum concentration to 3 to 4 hours, but does not alter the extent of absorption.

Distribution: The mean apparent volume of distribution (Vd/F) of pioglitazone following single-dose administration is 0.63 ± 0.41 (mean ± SD) L/kg of body weight. Pioglitazone is extensively protein bound (> 99%) in human serum, principally to serum albumin. Pioglitazone also binds to other serum proteins, but with lower affinity. Metabolites M-III and M-IV also are extensively bound (> 98%) to serum albumin.

Metabolism: Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates. Metabolites M-II and M-IV (hydroxy derivatives of pioglitazone) and M-III (keto derivative of pioglitazone) are pharmacologically active in animal models of type 2 diabetes. In addition to pioglitazone, M-III and M-IV are the principal drug-related species found in human serum following multiple dosing. At steady-state, in both healthy volunteers and in patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the total peak serum concentrations and 20% to 25% of the total AUC.

Pioglitazone incubated with expressed human P450 or human liver microsomes results in the formation of M-IV and to a much lesser degree, M-II. The major cytochrome P450 isoforms involved in the hepatic metabolism of pioglitazone are CYP2C8 and CYP3A4 with contributions from a variety of other isoforms including the mainly extrahepatic CYP1A1. Ketoconazole inhibited up to 85% of hepatic pioglitazone metabolism in vitro at a concentration equal molar to pioglitazone. Pioglitazone did not inhibit P450 activity when incubated with human P450 liver microsomes. In vivo human studies have not been performed to investigate any induction of CYP3A4 by pioglitazone.

Excretion and Elimination: Following oral administration, approximately 15% to 30% of the pioglitazone dose is recovered in the urine. Renal elimination of pioglitazone is negligible, and the drug is excreted primarily as metabolites and their conjugates. It is presumed that most of the oral dose is excreted into the bile either unchanged or as metabolites and eliminated in the feces.

The mean serum half-life of pioglitazone and total pioglitazone ranges from 3 to 7 hours and 16 to 24 hours, respectively. Pioglitazone has an apparent clearance, CL/F, calculated to be 5 to 7 L/hr.

Special Populations

Renal Insufficiency: The serum elimination half-life of pioglitazone, M-III, and M-IV remains unchanged in patients with moderate (creatinine clearance 30 to 60 mL/min) to severe (creatinine clearance < 30 mL/min) renal impairment when compared to normal subjects. No dose adjustment in patients with renal dysfunction is recommended (see DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: Compared with normal controls, subjects with impaired hepatic function (Child-Pugh Grade B/C) have an approximate 45% reduction in pioglitazone and total pioglitazone mean peak concentrations but no change in the mean AUC values.

ACTOS therapy should not be initiated if the patient exhibits clinical evidence of active liver disease or serum transaminase levels (ALT) exceed 2.5 times the upper limit of normal (see PRECAUTIONS, Hepatic Effects).

Elderly: In healthy elderly subjects, peak serum concentrations of pioglitazone and total pioglitazone are not significantly different, but AUC values are slightly higher and the terminal half-life values slightly longer than for younger subjects. These changes were not of a magnitude that would be considered clinically relevant.

Pediatrics: Pharmacokinetic data in the pediatric population are not available.

Gender: The mean C_{max} and AUC values were increased 20% to 60% in females. As monotherapy and in combination with sulfonylurea, metformin, or insulin, ACTOS improved glycemic control in both males and females. In controlled clinical trials, hemoglobin A_{1c} (HbA_{1c}) decreases from baseline were generally greater for females than for males (average mean difference in HbA_{1c} 0.5%). Since therapy should be individualized for each patient to achieve glycemic control, no dose adjustment is recommended based on gender alone.

Ethnicity: Pharmacokinetic data among various ethnic groups are not available.

Drug-Drug Interactions

The following drugs were studied in healthy volunteers with a co-administration of ACTOS 45 mg once daily. Listed below are the results:

Fexofenadine HCl: Co-administration of ACTOS for 7 days with 60 mg fexofenadine administered orally twice daily resulted in no significant effect on pioglitazone pharmacokinetics. ACTOS had no significant effect on fexofenadine pharmacokinetics.

Glipizide: Co-administration of ACTOS and 5 mg glipizide administered orally once daily for 7 days did not alter the steady-state pharmacokinetics of glipizide.

Digoxin: Co-administration of ACTOS with 0.25 mg digoxin administered orally once daily for 7 days did not alter the steady-state pharmacokinetics of digoxin.

Warfarin: Co-administration of ACTOS for 7 days with warfarin did not alter the steady-state pharmacokinetics of warfarin. ACTOS has no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy.
Metformin: Co-administration of a single dose of metformin (1000 mg) and ACTOS after 7 days of ACTOS did not alter the pharmacokinetics of the single dose of metformin.
Midazolam: Administration of ACTOS for 15 days followed by a single 7.5 mg dose of midazolam syrup resulted in a 26% reduction in midazolam C_{max} and AUC.
Ranitidine HCl: Co-administration of ACTOS for 7 days with ranitidine administered orally twice daily for either 4 or 7 days resulted in no significant effect on pioglitazone pharmacokinetics. ACTOS showed no significant effect on ranitidine pharmacokinetics.
Nifedipine ER: Co-administration of ACTOS for 7 days with 30 mg nifedipine ER administered orally once daily for 4 days to male and female volunteers resulted in a $\log_e$ transformed AUC ratio of 0.88 (CI 0.81 - 0.95). In view of the high variability of nifedipine pharmacokinetics, the clinical significance of this finding is unknown.
Oral Contraceptives: See **PRECAUTIONS**
Cytochrome P450: See **PRECAUTIONS**

Pharmacodynamics and Clinical Effects
Clinical studies demonstrate that ACTOS improves insulin sensitivity in insulin-resistant patients. ACTOS enhances cellular responsiveness to insulin, increases insulin-dependent glucose disposal, improves hepatic sensitivity to insulin, and improves dysfunctional glucose homeostasis. In patients with type 2 diabetes, the decreased insulin resistance produced by ACTOS results in lower blood glucose concentrations, lower plasma insulin levels, and lower HbA_{1c} values. Based on results from an open-label extension study, the glucose lowering effects of ACTOS appear to persist for at least one year. In controlled clinical trials, ACTOS in combination with sulfonylurea, metformin, or insulin had an additive effect on glycemic control.

Patients with lipid abnormalities were included in clinical trials with ACTOS. Overall, patients treated with ACTOS had mean decreases in triglycerides, mean increases in HDL cholesterol, and no consistent mean changes in LDL and total cholesterol.

In a 26-week, placebo-controlled, dose-ranging study, mean triglyceride levels decreased in the 15 mg, 30 mg, and 45 mg ACTOS dose groups compared to a mean increase in the placebo group. Mean HDL levels increased to a greater extent in patients treated with ACTOS than in the placebo-treated patients. There were no consistent differences for LDL and total cholesterol in patients treated with ACTOS compared to placebo (Table 1).

Table 1 **Lipids in a 26-Week Placebo-Controlled Dose-Ranging Study**

	Placebo	ACTOS 15 mg Once Daily	ACTOS 30 mg Once Daily	ACTOS 45 mg Once Daily
Triglycerides (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	262.8	283.8	261.1	259.7
Percent change from baseline (mean)	4.8%	-9.0%	-9.6%	-9.3%
HDL Cholesterol (mg/dL)	N=79	N=79	N=83	N=77
Baseline (mean)	41.7	40.4	40.8	40.7
Percent change from baseline (mean)	8.1%	14.1%	12.2%	19.1%
LDL Cholesterol (mg/dL)	N=65	N=63	N=74	N=62
Baseline (mean)	138.8	131.9	135.6	126.8
Percent change from baseline (mean)	4.8%	7.2%	5.2%	6.0%
Total Cholesterol (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	224.6	220.0	222.7	213.7
Percent change from baseline (mean)	4.4%	4.6%	3.3%	6.4%

In the two other monotherapy studies (24 weeks and 16 weeks) and in combination therapy studies with sulfonylurea (16 weeks) and metformin (16 weeks), the results were generally consistent with the data above. For patients treated with ACTOS, the placebo-corrected mean changes from baseline decreased 5% to 26% for triglycerides and increased 6% to 13% for HDL cholesterol.

In the combination therapy study with insulin (16 weeks), the placebo-corrected mean percent change from baseline in triglyceride values for patients treated with ACTOS was also decreased. A placebo-corrected mean change from baseline in LDL cholesterol of 7% was observed for the 15 mg dose group. Similar results to those noted above for HDL and total cholesterol were observed.

Clinical Studies

Monotherapy

In the U.S., three randomized, double-blind, placebo-controlled trials with durations from 16 to 26 weeks were conducted to evaluate the use of ACTOS as monotherapy in patients with type 2 diabetes. These studies examined ACTOS at doses up to 45 mg or placebo once daily in 865 patients.

In a 26-week dose-ranging study, 408 patients with type 2 diabetes were randomized to receive 7.5 mg, 15 mg, 30 mg, or 45 mg of ACTOS, or placebo once daily. Therapy with any previous antidiabetic agent was discontinued 8 weeks prior to the double-blind period. Treatment with 15 mg, 30 mg, and 45 mg of ACTOS produced statistically significant improvements in HbA_{1c} and fasting blood glucose (FBG) at endpoint compared to placebo (see Figure 1, Table 2).

Figure 1 shows the time course for changes in FBG and HbA_{1c} for the entire study population in this 26-week study.

Figure 1 Mean Change from Baseline for FBG and HbA_{1c} in a 26-Week Placebo-Controlled Dose-Ranging Study

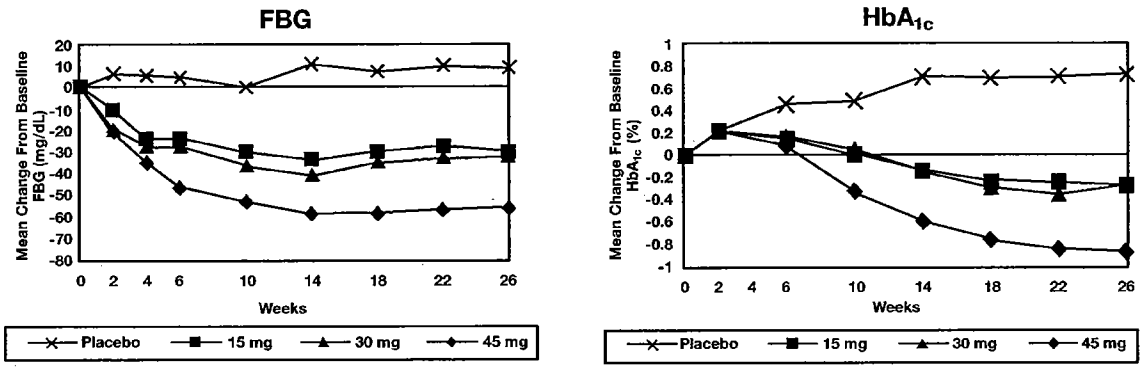


Table 2 shows HbA_{1c} and FBG values for the entire study population.

Table 2 Glycemic Parameters in a 26-Week Placebo-Controlled Dose-Ranging Study

	Placebo	ACTOS 15 mg Once Daily	ACTOS 30 mg Once Daily	ACTOS 45 mg Once Daily
Total Population				
HbA_{1c} (%)	N=79	N=79	N=85	N=76
Baseline (mean)	10.4	10.2	10.2	10.3
Change from baseline (adjusted mean[+])	0.7	-0.3	-0.3	-0.9
Difference from placebo (adjusted mean[+])		-1.0*	-1.0*	-1.6*
FBG (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	268	267	269	276
Change from baseline (adjusted mean[+])	9	-30	-32	-56
Difference from placebo (adjusted mean[+])		-39*	-41*	-65*

[+] Adjusted for baseline, pooled center, and pooled center by treatment interaction
*$p \leq 0.050$ vs. placebo

The study population included patients not previously treated with antidiabetic medication (naïve; 31%) and patients who were receiving antidiabetic medication at the time of study enrollment (previously treated; 69%). The data for the naïve and previously-treated patient subsets are shown in Table 3. All patients entered an 8 week washout/run-in period prior to double-blind treatment. This run-in period was associated with little change in HbA_{1c} and FBG values from screening to baseline for the naïve patients; however, for the previously-treated group, washout from previous antidiabetic medication resulted in deterioration of glycemic control and increases in HbA_{1c} and FBG. Although most patients in the previously-treated group had a decrease from baseline in HbA_{1c} and FBG with ACTOS, in many cases the values did not return to screening levels by the end of the study. The study design did not permit the evaluation of patients who switched directly to ACTOS from another antidiabetic agent.

Table 3 Glycemic Parameters in a 26-Week Placebo-Controlled Dose-Ranging Study

	Placebo	ACTOS 15 mg Once Daily	ACTOS 30 mg Once Daily	ACTOS 45 mg Once Daily
Naïve to Therapy				
HbA_{1c} (%)	N=25	N=26	N=26	N=21
Screening (mean)	9.3	10.0	9.5	9.8
Baseline (mean)	9.0	9.9	9.3	10.0
Change from baseline (adjusted mean*)	0.6	-0.8	-0.6	-1.9
Difference from placebo (adjusted mean*)		-1.4	-1.3	-2.6
FBG (mg/dL)	N=25	N=26	N=26	N=21
Screening (mean)	223	245	239	239
Baseline (mean)	229	251	225	235
Change from baseline (adjusted mean*)	16	-37	-41	-64
Difference from placebo (adjusted mean*)		-52	-56	-80
Previously Treated				
HbA_{1c} (%)	N=54	N=53	N=59	N=55
Screening (mean)	9.3	9.0	9.1	9.0
Baseline (mean)	10.9	10.4	10.4	10.6
Change from baseline (adjusted mean*)	0.8	-0.1	-0.0	-0.6
Difference from placebo (adjusted mean*)		-1.0	-0.9	-1.4
FBG (mg/dL)	N=54	N=53	N=58	N=56
Screening (mean)	222	209	230	215
Baseline (mean)	285	275	286	292
Change from baseline (adjusted mean*)	4	-32	-27	-55
Difference from placebo (adjusted mean*)		-36	-31	-59

* Adjusted for baseline and pooled center

In a 24-week study, 260 patients with type 2 diabetes were randomized to one of two forced-titration ACTOS treatment groups or a mock titration placebo group. Therapy with any previous antidiabetic agent was discontinued 6 weeks prior to the double-blind period. In one ACTOS treatment group, patients received an initial dose of 7.5 mg once daily. After four weeks, the dose was increased to 15 mg once daily and after another four weeks, the dose was increased to 30 mg once daily for the remainder of the study (16 weeks). In the second ACTOS treatment group, patients received an initial dose of 15 mg once daily and were titrated to 30 mg once daily and 45 mg once daily in a similar manner. Treatment with ACTOS, as described, produced statistically significant improvements in HbA_{1c} and FBG at endpoint compared to placebo (see Table 4).

Table 4 Glycemic Parameters in a 24-Week Placebo-Controlled Forced-Titration Study

	Placebo	ACTOS 30 mg[+] Once Daily	ACTOS 45 mg[+] Once Daily
Total Population			
HbA_{1c} (%)	N=83	N=85	N=85
Baseline (mean)	10.8	10.3	10.8
Change from baseline (adjusted mean[++])	0.9	-0.6	-0.6
Difference from placebo (adjusted mean[++])		-1.5*	-1.5*
FBG (mg/dL)	N=78	N=82	N=85
Baseline (mean)	279	268	281
Change from baseline (adjusted mean[++])	18	-44	-50
Difference from placebo (adjusted mean[++])		-62*	-68*

[+] Final dose in forced titration
[++] Adjusted for baseline, pooled center, and pooled center by treatment interaction
* $p \leq 0.050$ vs. placebo

For patients who had not been previously treated with antidiabetic medication (24%), mean values at screening were 10.1% for HbA_{1c} and 238 mg/dL for FBG. At baseline, mean HbA_{1c} was 10.2% and mean FBG was 243 mg/dL. Compared with placebo, treatment with ACTOS titrated to a final dose of 30 mg and 45 mg resulted in reductions from baseline in mean HbA_{1c} of 2.3% and 2.6% and mean FBG of 63 mg/dL and 95 mg/dL, respectively. For patients who had been previously treated with antidiabetic medication (76%), this medication was discontinued at screening. Mean values at screening were 9.4% for HbA_{1c} and 216 mg/dL for FBG. At baseline, mean HbA_{1c} was 10.7% and mean FBG was 290 mg/dL. Compared with placebo, treatment with ACTOS titrated to a final dose of 30 mg and 45 mg resulted in reductions from baseline in mean HbA_{1c} of 1.3% and 1.4% and mean FBG of 55 mg/dL and 60 mg/dL, respectively. For many previously-treated patients, HbA_{1c} and FBG had not returned to screening levels by the end of the study.

In a 16-week study, 197 patients with type 2 diabetes were randomized to treatment with 30 mg of ACTOS or placebo once daily. Therapy with any previous antidiabetic agent was discontinued 6 weeks prior to the double-blind period. Treatment with 30 mg of ACTOS produced statistically significant improvements in HbA_{1c} and FBG at endpoint compared to placebo (see Table 5).

Table 5 Glycemic Parameters in a 16-Week Placebo-Controlled Study

	Placebo	ACTOS 30 mg Once Daily
Total Population		
HbA_{1c} (%)	N=93	N=100
Baseline (mean)	10.3	10.5
Change from baseline (adjusted mean[+])	0.8	-0.6
Difference from placebo (adjusted mean[+])		-1.4*
FBG (mg/dL)	N=91	N=99
Baseline (mean)	270	273
Change from baseline (adjusted mean[+])	8	-50
Difference from placebo (adjusted mean[+])		-58*

[+] Adjusted for baseline, pooled center, and pooled center by treatment interaction
* $p \leq 0.050$ vs. placebo

For patients who had not been previously treated with antidiabetic medication (40%), mean values at screening were 10.3% for HbA_{1c} and 240 mg/dL for FBG. At baseline, mean HbA_{1c} was 10.4% and mean FBG was 254 mg/dL. Compared with placebo, treatment with ACTOS 30 mg resulted in reductions from baseline in mean HbA_{1c} of 1.0% and mean FBG of 62 mg/dL. For patients who had been previously treated with antidiabetic medication (60%), this medication was discontinued at screening. Mean values at screening were 9.4% for HbA_{1c} and 216 mg/dL for FBG. At baseline, mean HbA_{1c} was 10.6% and mean FBG was 287 mg/dL. Compared with placebo, treatment with ACTOS 30 mg resulted in reductions from baseline in mean HbA_{1c} of 1.3% and mean FBG of 46 mg/dL. For many previously-treated patients, HbA_{1c} and FBG had not returned to screening levels by the end of the study.

Combination Therapy

Three 16-week, randomized, double-blind, placebo-controlled clinical studies were conducted to evaluate the effects of ACTOS on glycemic control in patients with type 2 diabetes who were inadequately controlled ($HbA_{1c} \geq 8\%$) despite current therapy with a sulfonylurea, metformin, or insulin. Previous diabetes treatment may have been monotherapy or combination therapy.

In one combination study, 560 patients with type 2 diabetes on a sulfonylurea, either alone or combined with another antidiabetic agent, were randomized to receive 15 mg or 30 mg of ACTOS or placebo once daily in addition to their current sulfonylurea regimen. Any other antidiabetic agent was withdrawn. Compared with placebo, the addition of ACTOS to the sulfonylurea significantly reduced the mean HbA_{1c} by 0.9% and 1.3% for the 15 mg and 30 mg doses, respectively. Compared with placebo, mean FBG decreased by 39 mg/dL (15 mg dose) and 58 mg/dL (30 mg dose). The therapeutic effect of ACTOS in combination with sulfonylurea was observed in patients regardless of whether the patients were receiving low, medium, or high doses of sulfonylurea (< 50%, 50%, or > 50% of the recommended maximum daily dose).

In a second combination study, 328 patients with type 2 diabetes on metformin either alone or combined with another antidiabetic agent, were randomized to receive either 30 mg of ACTOS or placebo once daily in addition to their metformin. Any other

antidiabetic agent was withdrawn. Compared to placebo, the addition of ACTOS to metformin significantly reduced the mean HbA_{1c} by 0.8% and decreased the mean FBG by 38 mg/dL. The therapeutic effect of ACTOS in combination with metformin was observed in patients regardless of whether the patients were receiving lower or higher doses of metformin (< 2000 mg per day or ≥ 2000 mg per day).

In a third combination study, 566 patients with type 2 diabetes receiving a median of 60.5 units per day of insulin, either alone or combined with another antidiabetic agent, were randomized to receive either 15 mg or 30 mg of ACTOS or placebo once daily in addition to their insulin. Any other antidiabetic agent was discontinued. Compared to placebo, treatment with ACTOS in addition to insulin significantly reduced both HbA_{1c} (0.7% for the 15 mg dose and 1.0% for the 30 mg dose) and FBG (35 mg/dL for the 15 mg dose and 49 mg/dL for the 30 mg dose). The therapeutic effect of ACTOS in combination with insulin was observed in patients regardless of whether the patients were receiving lower or higher doses of insulin (< 60.5 units per day or ≥ 60.5 units per day).

INDICATIONS AND USAGE

ACTOS is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes (non-insulin-dependent diabetes mellitus, NIDDM). ACTOS is indicated for monotherapy. ACTOS is also indicated for use in combination with a sulfonylurea, metformin, or insulin when diet and exercise plus the single agent does not result in adequate glycemic control.

Management of type 2 diabetes should also include nutritional counseling, weight reduction as needed, and exercise. These efforts are important not only in the primary treatment of type 2 diabetes, but also to maintain the efficacy of drug therapy.

CONTRAINDICATIONS

ACTOS is contraindicated in patients with known hypersensitivity to this product or any of its components.

WARNINGS

Cardiac Failure and Other Cardiac Effects

ACTOS, like other thiazolidinediones, can cause fluid retention when used alone or in combination with other antidiabetic agents, including insulin. Fluid retention may lead to or exacerbate heart failure. Patients should be observed for signs and symptoms of heart failure (see Information for Patients). ACTOS should be discontinued if any deterioration in cardiac status occurs. Patients with New York Heart Association (NYHA) Class III and IV cardiac status were not studied during clinical trials; therefore, ACTOS is not recommended in these patients (see PRECAUTIONS, Cardiovascular).

In one 16-week U.S. double-blind, placebo-controlled clinical trial involving 566 patients with type 2 diabetes, ACTOS at doses of 15 mg and 30 mg in combination with insulin were compared to insulin therapy alone. This trial included patients with long-standing diabetes and a high prevalence of pre-existing medical conditions as follows: arterial hypertension (57.2%), peripheral neuropathy (22.6%), coronary heart disease (19.6%), retinopathy (13.1%), myocardial infarction (8.8%), vascular disease (6.4%),

angina pectoris (4.4%), stroke and/or transient ischemic attack (4.1%), and congestive heart failure (2.3%).

In this study two of the 191 patients receiving 15 mg ACTOS plus insulin (1.1%) and two of the 188 patients receiving 30 mg ACTOS plus insulin (1.1%) developed congestive heart failure compared with none of the 187 patients on insulin therapy alone. All four of these patients had previous histories of cardiovascular conditions including coronary artery disease, previous CABG procedures, and myocardial infarction.

Analysis of data from this study did not identify specific factors that predict increased risk of congestive heart failure on combination therapy with insulin.

PRECAUTIONS

General

ACTOS exerts its antihyperglycemic effect only in the presence of insulin. Therefore, ACTOS should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Hypoglycemia: Patients receiving ACTOS in combination with insulin or oral hypoglycemic agents may be at risk for hypoglycemia, and a reduction in the dose of the concomitant agent may be necessary.

Cardiovascular: In U.S. placebo-controlled clinical trials that excluded patients with New York Heart Association (NYHA) Class III and IV cardiac status, the incidence of serious cardiac adverse events related to volume expansion was not increased in patients treated with ACTOS as monotherapy or in combination with sulfonylureas or metformin vs. placebo-treated patients. In insulin combination studies, a small number of patients with a history of previously existing cardiac disease developed congestive heart failure when treated with ACTOS in combination with insulin (see WARNINGS). Patients with NYHA Class III and IV cardiac status were not studied in ACTOS clinical trials. ACTOS is not indicated in patients with NYHA Class III or IV cardiac status.

In postmarketing experience with ACTOS, cases of congestive heart failure have been reported in patients both with and without previously known heart disease.

Edema: ACTOS should be used with caution in patients with edema. In all U.S. clinical trials, edema was reported more frequently in patients treated with ACTOS than in placebo-treated patients (see ADVERSE REACTIONS). In postmarketing experience, reports of initiation or worsening of edema have been received.

Weight Gain: Dose related weight gain was seen with ACTOS alone and in combination with other hypoglycemic agents (Table 6). The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

Table 6 Weight Changes (kg) from Baseline during Double-Blind Clinical Trials with ACTOS

		Control Group (Placebo)	ACTOS 15 mg	ACTOS 30 mg	ACTOS 45 mg
		Median (25^{th} / 75^{th} percentile)	Median (25^{th} / 75^{th} percentile)	Median (25^{th} / 75^{th} percentile)	Median (25^{th} / 75^{th} percentile)
Monotherapy		-1.4 (-2.7/0.0) n=256	0.9 (-0.5/3.4) n=79	1.0 (-0.9/3.4) n=188	2.6 (0.2/5.4) n=79
Combination Therapy	Sulfonylurea	-0.5 (-1.8/0.7) n=187	2.0 (0.2/3.2) n=183	2.7 (1.1/4.5) n=186	N/A
	Metformin	-1.4 (-3.2/0.3) n=160	N/A	1.4 (-0.9/3.0) n=167	N/A
	Insulin	0.2 (-1.4/1.4) n=182	2.3 (0.5/4.3) n=190	3.6 (1.4/5.9) n=188	N/A

Ovulation: Therapy with ACTOS, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking ACTOS. Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been investigated in clinical studies so the frequency of this occurrence is not known.
Hematologic: ACTOS may cause decreases in hemoglobin and hematocrit. Across all clinical studies, mean hemoglobin values declined by 2% to 4% in patients treated with ACTOS. These changes primarily occurred within the first 4 to 12 weeks of therapy and remained relatively constant thereafter. These changes may be related to increased plasma volume and have not been associated with any significant hematologic clinical effects (see ADVERSE REACTIONS, Laboratory Abnormalities).
Hepatic Effects: Another drug of the thiazolidinedione class, troglitazone, has been associated with idiosyncratic hepatotoxicity, and very rare cases of liver failure, liver transplants, and death have been reported during postmarketing clinical use. In pre-approval controlled clinical trials in patients with type 2 diabetes, troglitazone was more frequently associated with clinically significant elevations of hepatic enzymes (ALT > 3 times the upper limit of normal) compared to placebo, and very rare cases of reversible jaundice were reported.

In pre-approval clinical studies worldwide, over 4500 subjects were treated with ACTOS. In U.S. clinical studies, over 2500 patients with type 2 diabetes received ACTOS. There was no evidence of drug-induced hepatotoxicity or elevation of ALT levels in the clinical studies.

During pre-approval placebo-controlled clinical trials in the U.S., a total of 4 of 1526 (0.26%) patients treated with ACTOS and 2 of 793 (0.25%) placebo-treated patients had ALT values $\geq$ 3 times the upper limit of normal. The ALT elevations in patients treated with ACTOS were reversible and were not clearly related to therapy with ACTOS.

In postmarketing experience with ACTOS, reports of hepatitis and of hepatic enzyme elevations to 3 or more times the upper limit of normal have been received. Very rarely, these reports have involved hepatic failure with and without fatal outcome, although causality has not been established.

Pioglitazone is structurally related to troglitazone, a thiazolidinedione no longer marketed in the United States, which was associated with idiosyncratic hepatotoxicity and rare cases of liver failure, liver transplants and death during postmarketing clinical use.

Pending the availability of the results of additional large, long-term controlled clinical trials and additional postmarketing safety data, it is recommended that patients treated with ACTOS undergo periodic monitoring of liver enzymes.

Serum ALT (alanine aminotransferase) levels should be evaluated prior to the initiation of therapy with ACTOS in all patients, every two months for the first year of therapy, and periodically thereafter. Liver function tests should also be obtained for patients if symptoms suggestive of hepatic dysfunction occur, e.g., nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine. The decision whether to continue the patient on therapy with ACTOS should be guided by clinical judgement pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued.

Therapy with ACTOS should not be initiated if the patient exhibits clinical evidence of active liver disease or the ALT levels exceed 2.5 times the upper limit of normal. Patients with mildly elevated liver enzymes (ALT levels at 1 to 2.5 times the upper limit of normal) at baseline or any time during therapy with ACTOS should be evaluated to determine the cause of the liver enzyme elevation. Initiation or continuation of therapy with ACTOS in patients with mildly elevated liver enzymes should proceed with caution and include appropriate clinical follow-up which may include more frequent liver enzyme monitoring. If serum transaminase levels are increased (ALT > 2.5 times the upper limit of normal), liver function tests should be evaluated more frequently until the levels return to normal or pretreatment values. If ALT levels exceed 3 times the upper limit of normal, the test should be repeated as soon as possible. If ALT levels remain > 3 times the upper limit of normal or if the patient is jaundiced, ACTOS therapy should be discontinued.

There are no data available to evaluate the safety of ACTOS in patients who experienced liver abnormalities, hepatic dysfunction, or jaundice while on troglitazone. ACTOS should not be used in patients who experienced jaundice while taking troglitazone.

Laboratory Tests

FBG and HbA_{1c} measurements should be performed periodically to monitor glycemic control and the therapeutic response to ACTOS.

Liver enzyme monitoring is recommended prior to initiation of therapy with ACTOS in all patients and periodically thereafter (see PRECAUTIONS, General, Hepatic Effects and ADVERSE REACTIONS, Serum Transaminase Levels).

Information for Patients

It is important to instruct patients to adhere to dietary instructions and to have blood glucose and glycosylated hemoglobin tested regularly. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be reminded to seek medical advice promptly.

Patients who experience an unusually rapid increase in weight or edema or who develop shortness of breath or other symptoms of heart failure while on ACTOS should immediately report these symptoms to their physician.

Patients should be told that blood tests for liver function will be performed prior to the start of therapy, every two months for the first year, and periodically thereafter. Patients

should be told to seek immediate medical advice for unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine.

Patients should be told to take ACTOS once daily. ACTOS can be taken with or without meals. If a dose is missed on one day, the dose should not be doubled the following day.

When using combination therapy with insulin or oral hypoglycemic agents, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.

Therapy with ACTOS, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking ACTOS. Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been investigated in clinical studies so the frequency of this occurrence is not known.

Drug Interactions

Oral Contraceptives: Administration of another thiazolidinedione with an oral contraceptive containing ethinyl estradiol and norethindrone reduced the plasma concentrations of both hormones by approximately 30%, which could result in loss of contraception. The pharmacokinetics of coadministration of ACTOS and oral contraceptives have not been evaluated in patients receiving ACTOS and an oral contraceptive. Therefore, additional caution regarding contraception should be exercised in patients receiving ACTOS and an oral contraceptive.

The cytochrome P450 isoform CYP3A4 is partially responsible for the metabolism of pioglitazone. Specific formal pharmacokinetic interaction studies have not been conducted with ACTOS and other drugs metabolized by this enzyme such as: erythromycin, astemizole, cisapride, corticosteroids, cyclosporine, HMG-CoA reductase inhibitors, tacrolimus, triazolam, and trimetrexate, as well as inhibitory drugs such as ketoconazole and itraconazole. In vitro, ketoconazole appears to significantly inhibit the metabolism of pioglitazone (see CLINICAL PHARMACOLOGY, Metabolism). Pending the availability of additional data, patients receiving ketoconazole concomitantly with ACTOS should be evaluated more frequently with respect to glycemic control.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A two-year carcinogenicity study was conducted in male and female rats at oral doses up to 63 mg/kg (approximately 14 times the maximum recommended human oral dose of 45 mg based on mg/m^2). Drug-induced tumors were not observed in any organ except for the urinary bladder. Benign and/or malignant transitional cell neoplasms were observed in male rats at 4 mg/kg/day and above (approximately equal to the maximum recommended human oral dose based on mg/m^2). The relationship of these findings in male rats to humans is unclear. A two-year carcinogenicity study was conducted in male and female mice at oral doses up to 100 mg/kg/day (approximately 11 times the maximum recommended human oral dose based on mg/m^2). No drug-induced tumors were observed in any organ.

During prospective evaluation of urinary cytology involving more than 1800 patients receiving ACTOS in clinical trials up to one year in duration, no new cases of bladder tumors were identified. Occasionally, abnormal urinary cytology results indicating possible malignancy were observed in both patients treated with ACTOS (0.72%) and patients treated with placebo (0.88%).

Pioglitazone HCl was not mutagenic in a battery of genetic toxicology studies, including the Ames bacterial assay, a mammalian cell forward gene mutation assay (CHO/HPRT and AS52/XPRT), an in vitro cytogenetics assay using CHL cells, an unscheduled DNA synthesis assay, and an in vivo micronucleus assay.

No adverse effects upon fertility were observed in male and female rats at oral doses up to 40 mg/kg pioglitazone HCl daily prior to and throughout mating and gestation (approximately 9 times the maximum recommended human oral dose based on mg/m^2).

Animal Toxicology

Heart enlargement has been observed in mice (100 mg/kg), rats (4 mg/kg and above) and dogs (3 mg/kg) treated orally with pioglitazone HCl (approximately 11, 1, and 2 times the maximum recommended human oral dose for mice, rats, and dogs, respectively, based on mg/m^2). In a one-year rat study, drug-related early death due to apparent heart dysfunction occurred at an oral dose of 160 mg/kg/day (approximately 35 times the maximum recommended human oral dose based on mg/m^2). Heart enlargement was seen in a 13-week study in monkeys at oral doses of 8.9 mg/kg and above (approximately 4 times the maximum recommended human oral dose based on mg/m^2), but not in a 52-week study at oral doses up to 32 mg/kg (approximately 13 times the maximum recommended human oral dose based on mg/m^2).

Pregnancy

Pregnancy Category C. Pioglitazone was not teratogenic in rats at oral doses up to 80 mg/kg or in rabbits given up to 160 mg/kg during organogenesis (approximately 17 and 40 times the maximum recommended human oral dose based on mg/m^2, respectively). Delayed parturition and embryotoxicity (as evidenced by increased postimplantation losses, delayed development and reduced fetal weights) were observed in rats at oral doses of 40 mg/kg/day and above (approximately 10 times the maximum recommended human oral dose based on mg/m^2). No functional or behavioral toxicity was observed in offspring of rats. In rabbits, embryotoxicity was observed at an oral dose of 160 mg/kg (approximately 40 times the maximum recommended human oral dose based on mg/m^2). Delayed postnatal development, attributed to decreased body weight, was observed in offspring of rats at oral doses of 10 mg/kg and above during late gestation and lactation periods (approximately 2 times the maximum recommended human oral dose based on mg/m^2).

There are no adequate and well-controlled studies in pregnant women. ACTOS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies, as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nursing Mothers

Pioglitazone is secreted in the milk of lactating rats. It is not known whether ACTOS is secreted in human milk. Because many drugs are excreted in human milk, ACTOS should not be administered to a breast-feeding woman.

Pediatric Use

Safety and effectiveness of ACTOS in pediatric patients have not been established.

Elderly Use
Approximately 500 patients in placebo-controlled clinical trials of ACTOS were 65 and over. No significant differences in effectiveness and safety were observed between these patients and younger patients.

ADVERSE REACTIONS

In worldwide clinical trials, over 3700 patients with type 2 diabetes have been treated with ACTOS. In U.S. clinical trials, over 2500 patients have received ACTOS, over 1100 patients have been treated for 6 months or longer, and over 450 patients for one year or longer.

The overall incidence and types of adverse events reported in placebo-controlled clinical trials of ACTOS monotherapy at doses of 7.5 mg, 15 mg, 30 mg, or 45 mg once daily are shown in Table 7.

Table 7 Placebo-Controlled Clinical Studies of ACTOS Monotherapy: Adverse Events Reported at a Frequency ≥ 5% of Patients Treated with ACTOS

(% of Patients)		
	Placebo N=259	ACTOS N=606
Upper Respiratory Tract Infection	8.5	13.2
Headache	6.9	9.1
Sinusitis	4.6	6.3
Myalgia	2.7	5.4
Tooth Disorder	2.3	5.3
Diabetes Mellitus Aggravated	8.1	5.1
Pharyngitis	0.8	5.1

For most clinical adverse events the incidence was similar for groups treated with ACTOS monotherapy and those treated in combination with sulfonylureas, metformin, and insulin. There was an increase in the occurrence of edema in the patients treated with ACTOS and insulin compared to insulin alone.

In the ACTOS plus insulin trial (n=379), 10 patients treated with ACTOS plus insulin developed dyspnea and also, at some point during their therapy, developed either weight change or edema. Seven of these 10 patients received diuretics to treat these symptoms. This was not reported in the insulin plus placebo group.

The incidence of withdrawals from clinical trials due to an adverse event other than hyperglycemia was similar for patients treated with placebo (2.8%) or ACTOS (3.3%).

Mild to moderate hypoglycemia was reported during combination therapy with sulfonylurea or insulin. Hypoglycemia was reported for 1% of placebo-treated patients and 2% of patients when ACTOS was used in combination with a sulfonylurea. In combination

with insulin, hypoglycemia was reported for 5% of placebo-treated patients, 8% for patients treated with 15 mg of ACTOS, and 15% for patients treated with 30 mg of ACTOS (see PRECAUTIONS, General, Hypoglycemia).

In U.S. double-blind studies, anemia was reported for 1.0% of patients treated with ACTOS and 0.0% of placebo-treated patients in monotherapy studies. Anemia was reported for 1.6% of patients treated with ACTOS and 1.6% of placebo-treated patients in combination with insulin. Anemia was reported for 0.3% of patients treated with ACTOS and 1.6% of placebo-treated patients in combination with sulfonylurea. Anemia was reported for 1.2% of patients treated with ACTOS and 0.0% of placebo-treated patients in combination with metformin.

In monotherapy studies, edema was reported for 4.8% of patients treated with ACTOS versus 1.2% of placebo-treated patients. In combination therapy studies, edema was reported for 7.2% of patients treated with ACTOS and sulfonylureas compared to 2.1% of patients on sulfonylureas alone. In combination therapy studies with metformin, edema was reported in 6.0% of patients on combination therapy compared to 2.5% of patients on metformin alone. In combination therapy studies with insulin, edema was reported in 15.3% of patients on combination therapy compared to 7.0% of patients on insulin alone. Most of these events were considered mild or moderate in intensity (see PRECAUTIONS, General, Edema).

In one 16-week clinical trial of insulin plus ACTOS combination therapy, more patients developed congestive heart failure on combination therapy (1.1%) compared to none on insulin alone (see WARNINGS, Cardiac Failure and Other Cardiac Effects).

Laboratory Abnormalities

Hematologic: ACTOS may cause decreases in hemoglobin and hematocrit. Across all clinical studies, mean hemoglobin values declined by 2% to 4% in patients treated with ACTOS. These changes generally occurred within the first 4 to 12 weeks of therapy and remained relatively stable thereafter. These changes may be related to increased plasma volume associated with ACTOS therapy and have not been associated with any significant hematologic clinical effects.

Serum Transaminase Levels: During placebo-controlled clinical trials in the U.S., a total of 4 of 1526 (0.26%) patients treated with ACTOS and 2 of 793 (0.25%) placebo-treated patients had ALT values $\geq$ 3 times the upper limit of normal. During all clinical studies in the U.S., 11 of 2561 (0.43%) patients treated with ACTOS had ALT values $\geq$ 3 times the upper limit of normal. All patients with follow-up values had reversible elevations in ALT. In the population of patients treated with ACTOS, mean values for bilirubin, AST, ALT, alkaline phosphatase, and GGT were decreased at the final visit compared with baseline. Fewer than 0.12% of patients treated with ACTOS were withdrawn from clinical trials in the U.S. due to abnormal liver function tests.

In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure (see PRECAUTIONS, Hepatic Effects).

CPK Levels: During required laboratory testing in clinical trials, sporadic, transient elevations in creatine phosphokinase levels (CPK) were observed. A single, isolated elevation to greater than 10 times the upper limit of normal (values of 2150 to 8610) was noted in 7 patients. Five of these patients continued to receive ACTOS and the other two patients had completed receiving study medication at the time of the elevated value. These

elevations resolved without any apparent clinical sequelae. The relationship of these events to ACTOS therapy is unknown.

OVERDOSAGE

During controlled clinical trials, one case of overdose with ACTOS was reported. A male patient took 120 mg per day for four days, then 180 mg per day for seven days. The patient denied any clinical symptoms during this period.

In the event of overdosage, appropriate supportive treatment should be initiated according to patient's clinical signs and symptoms.

DOSAGE AND ADMINISTRATION

ACTOS should be taken once daily without regard to meals.

The management of antidiabetic therapy should be individualized. Ideally, the response to therapy should be evaluated using HbA_{1c} which is a better indicator of long-term glycemic control than FBG alone. HbA_{1c} reflects glycemia over the past two to three months. In clinical use, it is recommended that patients be treated with ACTOS for a period of time adequate to evaluate change in HbA_{1c} (three months) unless glycemic control deteriorates.

Monotherapy

ACTOS monotherapy in patients not adequately controlled with diet and exercise may be initiated at 15 mg or 30 mg once daily. For patients who respond inadequately to the initial dose of ACTOS, the dose can be increased in increments up to 45 mg once daily. For patients not responding adequately to monotherapy, combination therapy should be considered.

Combination Therapy

Sulfonylureas: ACTOS in combination with a sulfonylurea may be initiated at 15 mg or 30 mg once daily. The current sulfonylurea dose can be continued upon initiation of ACTOS therapy. If patients report hypoglycemia, the dose of the sulfonylurea should be decreased.
Metformin: ACTOS in combination with metformin may be initiated at 15 mg or 30 mg once daily. The current metformin dose can be continued upon initiation of ACTOS therapy. It is unlikely that the dose of metformin will require adjustment due to hypoglycemia during combination therapy with ACTOS.
Insulin: ACTOS in combination with insulin may be initiated at 15 mg or 30 mg once daily. The current insulin dose can be continued upon initiation of ACTOS therapy. In patients receiving ACTOS and insulin, the insulin dose can be decreased by 10% to 25% if the patient reports hypoglycemia or if plasma glucose concentrations decrease to less than 100 mg/dL. Further adjustments should be individualized based on glucose-lowering response.

Maximum Recommended Dose

The dose of ACTOS should not exceed 45 mg once daily since doses higher than 45 mg once daily have not been studied in placebo-controlled clinical studies. No placebo-controlled clinical studies of more than 30 mg once daily have been conducted in combination therapy.

Dose adjustment in patients with renal insufficiency is not recommended (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Drug Metabolism).

Therapy with ACTOS should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT greater than 2.5 times the upper limit of normal) at start of therapy (see PRECAUTIONS, General, Hepatic Effects and CLINICAL PHARMACOLOGY, Special Populations, Hepatic Insufficiency). Liver enzyme monitoring is recommended in all patients prior to initiation of therapy with ACTOS and periodically thereafter (see PRECAUTIONS, General, Hepatic Effects).

There are no data on the use of ACTOS in patients under 18 years of age; therefore, use of ACTOS in pediatric patients is not recommended.

No data are available on the use of ACTOS in combination with another thiazolidinedione.

HOW SUPPLIED

ACTOS is available in 15 mg, 30 mg, and 45 mg tablets as follows:

15 mg Tablet: white to off-white, round, convex, non-scored tablet with "ACTOS" on one side, and "15" on the other, available in:

NDC 64764-151-04 Bottle of 30
NDC 64764-151-05 Bottle of 90
NDC 64764-151-06 Bottle of 500

30 mg Tablet: white to off-white, round, flat, non-scored tablet with "ACTOS" on one side, and "30" on the other, available in:

NDC 64764-301-14 Bottle of 30
NDC 64764-301-15 Bottle of 90
NDC 64764-301-16 Bottle of 500

45 mg Tablet: white to off-white, round, flat, non-scored tablet with "ACTOS" on one side, and "45" on the other, available in:

NDC 64764-451-24 Bottle of 30
NDC 64764-451-25 Bottle of 90
NDC 64764-451-26 Bottle of 500

STORAGE

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep container tightly closed, and protect from moisture and humidity.

Rx only

Manufactured by:
Takeda Chemical Industries, Ltd.
Osaka, Japan

Marketed by:
Takeda Pharmaceuticals America, Inc.
475 Half Day Road, Suite 500
Lincolnshire, IL 60069
and
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

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2002.3 – July 11, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-073/S-010

CLINICAL PHARMACOLOGY/ BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

NDA #:	21-073 SE8-010		
BRAND NAME:	ACTOS	**GENERIC NAME:**	Pioglitazone HCl
STRENGTH(S):	15, 30, and 45 mg	**DOSAGE FORM:**	Oral Tablet
APPLICANT:	Takeda Pharmaceuticals 475 Half Day Road, Suite 500, Lincolnshire, IL 60069		
OCPB DIVISION:	DPE-2	**ORM DIVISION:**	DMEDP
CPB REVIEWER:	Steven B. Johnson, Pharm.D.	**CPB TEAM LEADER:**	Hae-Young Ahn, Ph.D.

This submission is in response to an approvable (AE) letter that was issued to Takeda for NDA 21-073 SE8-010 on 04-JAN-2002 (refer to original review). The contents of this submission are related to the drug interaction labeling. Following are the suggestions that the Agency made to the Sponsor in the AE letter:

The following drugs were studied in healthy volunteers with a co-administration of ACTOS 45 mg once daily. Listed below are the results:

Fexofenadine HCl: Co-administration of ACTOS for 7 days with 60 mg fexofenadine administered orally twice daily resulted

Glipizide: Co-administration of ACTOS and 5 mg glipizide administered orally once daily for 7 days did not alter the steady-state pharmacokinetics of glipizide.

Digoxin: Co-administration of ACTOS with 0.25 mg digoxin administered orally once daily for 7 days did not alter the steady-state pharmacokinetics of digoxin.

Warfarin: Co-administration of ACTOS for 7 days with warfarin did not alter the steady-state pharmacokinetics of warfarin. ACTOS has no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy.

Metformin: Co-administration of a single dose of metformin (1000 mg) and ACTOS after 7 days of ACTOS did not alter the pharmacokinetics of the single dose of metformin.

Ranitidine HCl: Co-administration of ACTOS for 7 days with ranitidine administered orally twice daily for either 4 or 7 days resulted in a

Nifedipine ER: Co-administration of ACTOS for 7 days with 30 mg nifedipine ER administered orally once daily for 4 days

Ketoconazole: Co-administration of ACTOS and ketoconazole (200 mg)

Midazolam: Administration of ACTOS for 15 days followed by a single 7.5 mg dose of midazolam syrup resulted in a 26% reduction in midazolam C_{max} and AUC.

*Oral Contraceptives: See **PRECAUTIONS***

*Cytochrome P450: See **PRECAUTIONS***

***PRECAUTIONS** section, **Drug Interactions** subsection:*

Oral Contraceptives: Administration of another thiazolidinedione with an oral contraceptive containing ethinyl estradiol and norethindrone reduced the plasma concentrations of both hormones by approximately 30%, which could result in loss of contraception. The pharmacokinetics of co-administration of ACTOS and oral contraceptives have not been evaluated in patients receiving ACTOS and an oral contraceptive. Therefore, additional caution regarding contraception should be exercised in patients receiving ACTOS and an oral contraceptive.

The cytochrome P450 isoform CYP3A4 is partially responsible for the metabolism of pioglitazone. Specific formal pharmacokinetic interaction studies have not been conducted with ACTOS and other drugs metabolized by this enzyme such as: erythromycin, astemizole, cisapride, corticosteroids, cyclosporine, HMG-CoA reductase inhibitors, tacrolimus, triazolam, and trimetrexate, as well as inhibitory drugs such as ketoconazole and itraconazole. In vitro, ketoconazole appears to significantly inhibit the metabolism of pioglitazone (see CLINICAL PHARMACOLOGY, Metabolism). ~~Pending the availability of additional data, patients~~ Patients receiving ketoconazole concomitantly with ACTOS should be evaluated more frequently with respect to glycemic control.

ISSUES

1)

Agency Response

- In Section V of the Guidance for Industry entitled, "In vivo drug metabolism/drug interaction studies – ," it states that "all relevant information on the metabolic pathways and metabolites and pharmacokinetic interaction should be included in the CLINICAL PHARMACOLOGY section of the labeling. The consequences of metabolism and interactions should be placed in PRECAUTIONS/WARNINGS, CONTRAINDICATIONS, AND DOSAGE ADMINISTRATION sections, as appropriate." Therefore, the Agency recommends that the drug-drug interaction information be placed under CLINICAL PHARMACOLOGY as suggested in the 04-JAN-2002 Approvable Letter and under the PRECAUTIONS section.

2) The Sponsor suggests that the following statement be used in lieu of the Agency's recommendation for:

Fexofenadine HCl:

Agency Response

- Fexofenadine HCl: Co-administration of ACTOS for 7 days with 60 mg fexofenadine administered orally twice daily resulted in no significant effect on pioglitazone pharmacokinetics. ACTOS had no significant effect on fexofenadine pharmacokinetics.

3) The Sponsor suggests that the following statement be used in lieu of the Agency's recommendation for:

Ranitidine HCl:

Agency Response

- Ranitidine HCl: Co-administration of ACTOS for 7 days with ranitidine administered orally twice daily for either 4 or 7 days resulted in no significant effect on pioglitazone pharmacokinetics. ACTOS showed no significant effect on ranitidine pharmacokinetics.

4) The Sponsor suggests that the following statement be used in lieu of the Agency's recommendation for:

Nifedipine ER: [redacted]

Agency Response

- Nifedipine ER: Co-administration of ACTOS for 7 days with 30 mg nifedipine ER administered orally once daily for 4 days. [redacted]

5) The Sponsor requests that the information that the Agency recommend regarding the ketoconazole and pioglitazone drug interaction study not be included at this time.

Agency Response

- The Agency agrees that this data will not be included in the labeling at this time. However, this issue will be addressed in the Sponsor's March 2002 submission and labeling will be changed as necessary.

NOTE:
Please convey the responses listed above to the sponsor as appropriate.

Steven B. Johnson, Pharm.D.
CPB Reviewer

Hae-Young Ahn, Ph.D.
CPB Team Leader

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Steve Johnson
7/8/02 04:09:10 PM
BIOPHARMACEUTICS

Hae-Young Ahn
7/8/02 05:59:50 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-073 SE8-010	**RELEVANT IND**:	33,729 (N344)
BRAND NAME:	ACTOS®	**GENERIC NAME**:	Pioglitazone hydrochloride
STRENGTH(S):	15 mg, 30 mg, and 45 mg tablets		
SPONSOR:	Takeda Pharmaceuticals North America, Inc 475 Half Day Road – Suite 500, Lincolnshire, IL 60069		
SUBMISSION DATE:	2-MAR-2001		
CPB REVIEWER:	Steven B. Johnson, Pharm.D.		
CPB TEAM LEADER:	Hae-Young Ahn, Ph.D.		

SYNOPSIS

Takeda Pharmaceuticals North America has submitted supplemental NDA 21-073 (SE8-010) for ACTOS® (pioglitzone hydrochloride) Tablets. This supplement consists of three 3-way crossover design drug-drug interaction studies that compare a steady-state dose of ACTOS® 45 mg administered orally once daily with a steady-state dose of: ALLEGRA™ (fexofenadine hydrochloride) 60 mg administered orally twice daily; ZANTAC® (ranitidine hydrochloride) 150 mg administered orally twice daily; and PROCARDIA® XL (nifedipine extended release) 30 mg administered orally once daily.

This submission is part 2 of two sets of recent drug interaction studies submitted for review; part 1 consisted of two phase IV drug interaction studies (see **Appendix**). The Agency requested the phase IV commitment due to the results of the *in vitro* drug interaction studies, which showed that pioglitazone metabolism could be significantly inhibited (85%) by a cytochrome P450 3A4 (CYP3A4) inhibitor, ketoconazole, and that another member of the thiazolidinedione drug class, troglitazone, was a CYP3A4 inducer. The results of the phase IV studies will not be discussed in this review, however, they will be incorporated into the new proposed labeling for ACTOS®.

The studies outlined above were conducted to determine what effects these drugs had on unchanged pioglitazone, total pioglitazone, and on the pioglitazone metabolites, III and IV, and what effect(s) pioglitazone hydrochloride had on these drugs. These studies are relevant in that they attempt to address the characteristics that pioglitazone is thought to possess with regard to cytochrome P450 (CYP) metabolism and its potential effect on efflux transporters (e.g., PGP). Induction, however, was the principal theme as characterized by the steady-state nature of the study designs.

Study **PNFP-037** evaluated what effect pioglitazone had on fexofenadine, and vice versa. Given that fexofenadine is thought to be a PGP substrate, and pioglitazone may have a propensity to alter the PGP efflux transporter, the results of this study had a potential of great consequence. Co-administration of ACTOS® for seven days with ALLEGRA® resulted in a 37% and 29% increase in the evening (PM) fexofenadine C_{max} and AUC, respectively. There was no alteration in either the morning fexofenadine levels or the pioglitazone measures. These results were not found to be clinically significant because the total exposure, as measured by AUC, of fexofenadine PM was still considerably less than that seen after a morning (AM) dose.

Study **PNFP-038** described the relationship between pioglitazone and ranitidine. Co-administration of ACTOS® for 7 days with ZANTAC™ for either 4 or 7 days resulted in a 16% and 13% reduction in unchanged pioglitazone C_{max} and AUC levels. There was also a significant gender-by-treatment interaction detected between the AM and PM ranitidine concentrations. The AM and PM ranitidine AUC and C_{max} were reduced by about 10% in males and increased by about 10% in females. Again, these results are not thought to be clinically relevant.

The final study, **PNFP-040.1**, examined pioglitazone in combination with an extended release formulation of nifedipine. Co-administration of ACTOS® for 7 days with PROCARDIA® XL for either 4 or 7 days

resulted in a 25% reduction in nifedipine C_{max} and 21% reduction in AUC for male subjects. Female subjects showed an 8% decrease in C_{max}, but there was no difference in total exposure between the treatments.

In conclusion, the results of these three studies were rather unremarkable, with nifedipine ER being the most significant of the described drug interactions. However, the Medical Officer should comment on the clinical relevance of each of these findings.

RECOMMENDATION

It is the recommendation of the Office of Clinical Pharmacology and Biopharmaceutics that the findings of these studies, along with the results of the two phase IV studies, be incorporated into the labeling for ACTOS® tablets.

BIOANALYTICAL ASSAYS

Unchanged pioglitazone and the two metabolites, M-III and M-IV, were analyzed / ——— / using a validated method developed / ——— / for studies PNFP-037,–038, and –040.1. The study samples were analyzed using an HPLC with UV absorbance. Calibration, precision, and accuracy were all found to be acceptable for the parent and the metabolites. However, the upper quality control accuracy values, theoretical value = 2000 ng/mL, are pushing the bounds of acceptability in study PNFP-037 for the parent and M-III metabolite. Results of the quality control testing are as follows:

Pioglitzone									
Study #:	**PNFP-037**			**PNFP-038**			**PNFP-040.1**		
Type:	Parent	M-III	M-IV	Parent	M-III	M-IV	Parent	M-III	M-IV
Calibration (ng/mL):	25.0 – 2500	25.0 – 2500	25.0 – 2500	25.0 – 2500	25.0 – 2500	25.0 – 2500	25.0 – 2500	25.0 – 2500	25.0 – 2500
LLOQ (ng/mL):	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0
Precision (%RSD):									
75.0	9.5	8.3	8.4	10.3	6.9	9.5	7.3	4.5	6.5
375	10.5	9.3	6.5	8.8	7.9	6.8	5.0	4.8	3.6
2000	7.8	6.7	6.8	6.7	5.7	5.4	5.2	5.2	4.4
5000				2.3	5.8	6.9			
Accuracy (%):									
75.0	102.9	100.8	108.7	105.6	101.3	106.3	99.2	91.3	100.3
375	101.4	100.9	109.7	103.0	100.2	108.3	102.4	94.4	101.3
2000	89.3	86.6	101.0	96.2	89.6	101.1	100.0	89.0	97.5
5000				98.5	92.6	101.8			

Ranitidine and fexofenadine plasma samples were analyzed using validated HPLC methods with MS detection, and nifedipine samples were analyzed using a validated gas chromatography method with electron capture detection.

Study #:	**Fexofenadine: PNFP-037**		**Ranitidine: PNFP-038**		**Nifedipine: PNFP-040.1**	
Calibration (ng/mL):	10.0 – 1000		10.0 – 1000		0.500 – 200	
LLOQ (ng/mL):	10.0		10.0		0.500	
Precision (%RSD):			**40.0**	8.4		
	45.0	10.8	**250**	11.1	**2.0**	11.1
	150	9.9	**749**	8.6	**40.0**	6.6
	750	10.4	**2020**	–	**150**	7.6
Accuracy (%):			**40.0**	101.4		
	45.0	91.9	**250**	100.7	**2.0**	106.7
	150	102.6	**749**	98.9	**40.0**	98.4
	750	99.5	**2020**	84.2	**150**	101.8

DRUG INTERACTION STUDIES

Three drug interaction studies were submitted to this supplemental application. Each of these studies was an open-label, three-treatment, two-sequence, crossover design. Objectives common to each study were: to determine the effect of steady-state pioglitazone levels on the steady-state PK of drug X; to determine the effect of steady-state drug X levels on the steady-state PK of pioglitazone, including pioglitazone metabolites; and to examine gender differences.

The first study, **PNFP-037**, evaluated the steady-state PK of pioglitazone (unchanged, total, and metabolites III and IV) on the steady-state PK of fexofenadine, and vice versa. Twenty-four (23 completers: 11 male & 12 female) healthy subjects were administered one 15 mg and one 30 mg pioglitazone HCl tablet orally once daily in the morning for 7 days (**Tx A**), one 60 mg fexofenadine HCl capsule twice daily (once in the morning and once in the evening) for 7 days (**Tx B**), and a combination of treatments A and B for 7 days (**Tx C**) in one of two sequences: SEQ 1 = Tx A, Tx B, Tx C, or SEQ 2 = Tx B, Tx C, Tx A. There was no washout between periods 1 and 2, and a 10-day washout between the last dose of Period 2 and the first dose of Period 3. Results of study **PNFP-037** are presented in tables 2 through 7.

Table 2: Unchanged Pioglitazone: Pioglitazone Alone (Tx A) Vs. Pioglitazone plus Fexofenadine (Tx C)

Parameter	Tx A	Tx C	T/R	90% CI
C_{max} (ng/mL)	1568 ± 516.5	1596 ± 622.1	102	92.5 – 111
ln C_{max}	1467	1468	**100**	**89.9 – 111**
T_{max} (hr)	2.00 (1.00 – 4.00)	2.00 (1.00 – 4.00)	102	--
C_{min} (ng/mL)	215 ± 100.6	200 ± 89.7	93.0	83.0 – 103
AUC $_{0-t}$ (ng*hr/mL)	14933 ± 5108.9	15467 ± 6320.7	104	95.4 – 112
ln AUC $_{0-t}$	13907	14096	**101**	**93.6 – 110**
K_e (hr^{-1})	0.0578 ± 0.02164	0.0773 ± 0.03669	127	--
$t_{1/2}$ (hr)	13.7 ± 5.52	13.4 ± 11.53	101	--

Mean ± SD; Median (range); **Bold** = equivalence comparison

Table 3: Pioglitazone M-III Metabolite: Pioglitazone Alone (Tx A) Vs. Pioglitazone plus Fexofenadine (Tx C)

Parameter	Tx A	Tx C	T/R	90% CI
C_{max} (ng/mL)	551 ± 194.0	536 ± 181.3	97.3	87.5 – 107
ln C_{max}	514	502	**97.6**	**88.9 – 107**
T_{max} (hr)	4.00 (0.00 – 18.00)	4.00 (2.00 – 20.00)	119	--
C_{min} (ng/mL)	376 ± 143.0	385 ± 133.7	102	94.3 – 110
AUC $_{0-t}$ (ng*hr/mL)	10019 ± 3007.8	10502 ± 3670.2	105	98.5 – 111
ln AUC $_{0-t}$	9488	9792	**103**	**96.8 – 110**
K_e (hr^{-1})	--	--	--	--
$t_{1/2}$ (hr)	--	--	--	--

Mean ± SD; Median (range); **Bold** = equivalence comparison

Table 4: Pioglitazone M-IV Metabolite: Pioglitazone Alone (Tx A) Vs. Pioglitazone plus Fexofenadine (Tx C)

Parameter	Tx A	Tx C	T/R	90% CI
C_{max} (ng/mL)	1495 ± 354.6	1510 ± 352.7	101	94.7 – 107
ln C_{max}	1452	1471	**101**	**95.0 – 108**
T_{max} (hr)	8.00 (0.00 – 12.00)	10.0 (2.00 – 16.0)	109	--
C_{min} (ng/mL)	1085 ± 254.0	1091 ± 275.0	101	94.5 – 107
AUC $_{0-t}$ (ng*hr/mL)	29464 ± 6493.0	30398 ± 7518.3	103	97.9 – 108
ln AUC $_{0-t}$	28760	29538	**103**	**97.3 – 108**
K_e (hr^{-1})	--	--	--	--
$t_{1/2}$ (hr)	--	--	--	--

Mean ± SD; Median (range); **Bold** = equivalence comparison

Table 5: Total Pioglitazone: Pioglitazone Alone (Tx A) Vs. Pioglitazone plus Fexofenadine (Tx C)

Parameter	Tx A	Tx C	T/R	90% CI
C_{max} (ng/mL)	3395 ± 869.7	3466 ± 1021.6	102	94.7 – 110
ln C_{max}	3267	3309	**101**	**93.6 – 110**
T_{max} (hr)	3.00 (0.00 – 4.00)	3.00 (2.00 – 4.00)	95.7	--
C_{min} (ng/mL)	1676 ± 441.7	1676 ± 436.1	100	93.5 – 107
AUC $_{0-t}$ (ng*hr/mL)	54372 ± 12953.1	56183 ± 15669.9	103	97.4 – 109
ln AUC $_{0-t}$	52675	53912	**102**	**96.3 – 109**
K_e (hr^{-1})	--	--	--	--
$t_{1/2}$ (hr)	--	--	--	--

Mean ± SD; Median (range); **Bold** = equivalence comparison

Table 6: Fexofenadine AM: Fexofenadine Alone (Tx B) Vs. Fexofenadine plus Pioglitazone (Tx C)

Parameter	Tx B	Tx C	T/R	90% CI
C_{max} (ng/mL)	245 ± 112.4	229 ± 86.4	93.2	82.6 – 104
ln C_{max}	228	213	**93.8**	**85.3 – 103**
T_{max} (hr)	2.00 (1.00 – 6.00)	2.00 (1.00 – 6.00)	107	–
C_{min} (ng/mL)	33.6 ± 12.78	42.1 ± 16.40	122	106 – 137
AUC $_{0-t}$ (ng*hr/mL)	1289 ± 510.6	1368 ± 501.5	106	93.3 – 118
ln AUC $_{0-t}$	1216	1296	**107**	**95.0 – 119**
K_e (hr^{-1})	0.1803 ± 0.05638	0.1756 ± 0.07063	95.6	–
$t_{1/2}$ (hr)	4.47 ± 2.457	4.61 ± 2.057	107	–

Mean ± SD; Median (range); **Bold** = equivalence comparison

Table 7: Fexofenadine PM: Fexofenadine Alone (Tx B) Vs. Fexofenadine plus Pioglitazone (Tx C)

Parameter	Tx B	Tx C	T/R	90% CI
C_{max} (ng/mL)	153 ± 62.9	209 ± 86.4	135	112 – 157
ln C_{max}	142	194	**137**	**114 – 163**
T_{max} (hr)	3.00 (1.50 – 6.00)	2.50 (1.50 – 4.00)	85.6	–
C_{min} (ng/mL)	33.7 ± 11.71	44.7 ± 17.29	128	112 – 145
AUC $_{0-t}$ (ng*hr/mL)	853 ± 254.5	1124 ± 381.2	129	115 – 144
ln AUC $_{0-t}$	829	1075	**130**	**115 – 146**
K_e (hr^{-1})	0.1574 ± 0.04643	0.1406 ± 0.04456	91.9	–
$t_{1/2}$ (hr)	4.81 ± 1.1489	5.66 ± 2.648	111	–

Mean ± SD; Median (range); **Bold** = equivalence comparison

Comparisons of treatments A and C showed that the AUC and C_{max} were similar for unchanged pioglitazone, total pioglitazone, and pioglitazone metabolites, respectively. However, when treatments B and C were compared, there was a 37% and 30% increase in the PM fexofenadine C_{max} and AUC parameters, respectively, in treatment C. This result was somewhat puzzling given that there is no evidence of an interaction following the AM dose and the fact that both pioglitazone and fexofenadine are at steady-state. There is also considerable variability that appears to be inherent to fexofenadine in this study. Therefore, despite the apparent drug interaction seen with the PM dose of fexofenadine, a definitive conclusion regarding pioglitazone's ability to block or alter PGP cannot be made. In addition, since the value of the exposure metric AUC is considerably lower after PM dosing compared to the AM dosing, the clinical significance of this interaction is not likely to be significant.

The second study, **PNFP-038**, evaluated the steady-state PK of pioglitazone (unchanged, total, and metabolites III and IV) on the steady-state PK of ranitidine, and vice versa. Twenty-four (23 completers: 12 male & 11 female) healthy subjects were administered one 15 mg and one 30 mg pioglitazone HCl tablet orally once daily in the morning for 7 days (**Tx A**), one 150 mg ranitidine HCl capsule twice daily (once in the morning and once in the evening) for 4 days (**Tx B**), and a combination of treatments A and B for 4 days (**Tx C_1**) or 7 days (**Tx C_2**) in one of two sequences: SEQ 1 = Tx A, Tx C_1, Tx B, or SEQ 2 = Tx B, Tx C_2, Tx A. There was no washout between periods 1 and 2, and a 10-day washout between the last dose of Period 2 and the first dose of Period 3. Results of study **PNFP-038** are presented in tables 8 through 15.

Table 8: Unchanged Pioglitazone: Pioglitazone Alone (Tx A) Vs. Pioglitazone plus Ranitidine (Tx C)

Parameter	Tx A	Tx C	T/R	90% CI
C_{max} (ng/mL)	1616 ± 522.9	1346 ± 435.0	83.5	73.5 – 93.5
ln C_{max}	1524	1280	**84.0**	**74.6 – 94.6**
T_{max} (hr)	2.00 (1.00 – 4.00)	2.00 (1.00 – 4.00)	132	–
C_{min} (ng/mL)	168 ± 68.0	152 ± 75.4	93.7	85.9 – 102
AUC $_{0-t}$ (ng*hr/mL)	13801 ± 4252.7	11889 ± 3888.4	87.0	78.5 – 95.5
ln AUC $_{0-t}$	12918	11216	**86.8**	**78.3 – 96.2**
K_e (hr^{-1})	0.0621 ± 0.03383	0.0734 ± 0.03680	110	–
$t_{1/2}$ (hr)	13.7 ± 6.69	11.8 ± 5.72	91.1	–

Mean ± SD; Median (range); **Bold** = equivalence comparison

Table 9: Pioglitazone M-III Metabolite: Pioglitazone Alone (Tx A) Vs. Pioglitazone plus Ranitidine (Tx C)

Parameter	Tx A	Tx C	T/R	90% CI
C_{max} (ng/mL)	580 ± 183.3	499 ± 169.8	86.6	81.8 – 91.5
ln C_{max}	550	473	**86.0**	**81.1 – 91.1**
T_{max} (hr)	6.00 (3.00 – 12.00)	4.00 (3.00 – 20.00)	99	–
C_{min} (ng/mL)	381 ± 126.8	335 ± 125.0	88.5	82.8 – 94.2
AUC $_{0-t}$ (ng*hr/mL)	10678 ± 3547.1	9404 ± 3265.7	88.7	83.8 – 93.5
ln AUC $_{0-t}$	10075	8894	**88.3**	**83.2 – 93.7**
K_e (hr^{-1})	–	–	–	–
$t_{1/2}$ (hr)	–	–	–	–

Mean ± SD; Median (range); **Bold** = equivalence comparison

Table 10: Pioglitazone M-IV Metabolite: Pioglitazone Alone (Tx A) Vs. Pioglitazone plus Ranitidine (Tx C)

Parameter	Tx A	Tx C	T/R	90% CI
C_{max} (ng/mL)	1566 ± 353.1	1301 ± 300.6	83.3	78.2 – 88.4
ln C_{max}	1526	1269	**83.1**	**78.4 – 88.1**
T_{max} (hr)	10.0 (1.00 – 16.00)	10.0 (2.00 – 10.00)	85.8	–
C_{min} (ng/mL)	1106 ± 243.6	939 ± 241.5	85.6	79.6 – 91.5
AUC $_{0-t}$ (ng*hr/mL)	30608 ± 6441.8	26068 ± 6046.4	85.5	80.5 – 60.6
ln AUC $_{0-t}$	29821	25405	**85.2**	**80.1 – 90.6**
K_e (hr^{-1})	–	–	–	–
$t_{1/2}$ (hr)	–	–	–	–

Mean ± SD; Median (range); **Bold** = equivalence comparison

Table 11: Total Pioglitazone: Pioglitazone Alone (Tx A) Vs. Pioglitazone plus Ranitidine (Tx C)

Parameter	Tx A	Tx C	T/R	90% CI
C_{max} (ng/mL)	3403 ± 805.3	2986 ± 787.0	88.3	82.4 – 94.2
ln C_{max}	3293	2891	**87.8**	**81.8 – 94.2**
T_{max} (hr)	3.00 (1.00 – 4.00)	3.00 (1.00 – 4.00)	111	–
C_{min} (ng/mL)	1656 ± 387.6	1426 ± 401.8	87.0	81.6 – 92.5
AUC $_{0-t}$ (ng*hr/mL)	55074 ± 12904.1	47307 ± 11855.6	86.5	81.1 – 91.8
ln AUC $_{0-t}$	53202	45871	**86.2**	**80.7 – 92.1**
K_e (hr^{-1})	–	–	–	–
$t_{1/2}$ (hr)	–	–	–	–

Mean ± SD; Median (range); **Bold** = equivalence comparison

Table 12: Ranitidine AM (Males): Ranitidine Alone (Tx B) Vs. Ranitidine plus Pioglitazone (Tx C)

Parameter	Tx B	Tx C	T/R	90% CI
C_{max} (ng/mL)	559 ± 156.9	499 ± 87.4	89.2	74.4 – 104
ln C_{max}	539	492	**91.2**	**79.4 – 105**
T_{max} (hr)	3.25 (1.50 – 4.00)	2.75 (1.00 – 4.00)	86.3	–
C_{min} (ng/mL)	52.7 ± 16.31	44.7 ± 10.84	84.9	73.6 – 96.1
AUC $_{0-t}$ (ng*hr/mL)	2949 ± 710.5	2617 ± 323.8	88.8	75.2 – 102
ln AUC $_{0-t}$	2880	2601	**90.3**	**79.7 – 102**
K_e (hr^{-1})	0.2979 ± 0.03231	0.2992 ± 0.03717	100.0	–
$t_{1/2}$ (hr)	2.36 ± 0.290	2.35 ± 0.273	99.7	–

Mean ± SD; Median (range); **Bold** = equivalence comparison

Table 13: Ranitidine AM (Females): Ranitidine Alone (Tx B) Vs. Ranitidine plus Pioglitazone (Tx C)

Parameter	Tx B	Tx C	T/R	90% CI
C_{max} (ng/mL)	570 ± 165.0	649 ± 144.6	114	104 – 124
ln C_{max}	545	636	**117**	**103 – 132**
T_{max} (hr)	2.25 (1.00 – 4.00)	2.00 (1.00 – 4.00)	91.2	–
C_{min} (ng/mL)	43.0 ± 23.45	44.7 ± 17.40	104	84.9 – 123
AUC $_{0-t}$ (ng*hr/mL)	2880 ± 785.7	3106 ± 596.8	108	95.7 – 120
ln AUC $_{0-t}$	2782	3053	**110**	**95.4 – 126**
K_e (hr^{-1})	0.3107 ± 0.04422	0.3336 ± 0.04675	107	–
$t_{1/2}$ (hr)	2.28 ± 0.378	2.11 ± 0.272	92.7	–

Mean ± SD; Median (range); **Bold** = equivalence comparison

Table 14: Ranitidine PM (Males): Ranitidine Alone (Tx B) Vs. Ranitidine plus Pioglitazone (Tx C)

Parameter	Tx B	Tx C	T/R	90% CI
C_{max} (ng/mL)	480 ± 102.2	422 ± 85.8	88.0	74.8 – 101
ln C_{max}	470	414	**88.2**	**77.1 – 101**
T_{max} (hr)	3.00 (1.50 – 4.00)	3.75 (2.00 – 4.00)	113	--
C_{min} (ng/mL)	58.9 ± 21.94	55.5 ± 15.42	94.2	83.2 – 105
AUC $_{0-t}$ (ng*hr/mL)	2803 ± 614.6	2501 ± 258.1	89.2	76.8 – 102
ln AUC $_{0-t}$	55.1	53.4	**90.7**	**80.5 – 102**
K_e (hr^{-1})	0.2168 ± 0.03417	0.2059 ± 0.03121	95.0	--
$t_{1/2}$ (hr)	3.26 ± 0.437	3.44 ± 0.553	106.0	--

Mean ± SD; Median (range); **Bold** = equivalence comparison

Table 15: Ranitidine PM (Females): Ranitidine Alone (Tx B) Vs. Ranitidine plus Pioglitazone (Tx C)

Parameter	Tx B	Tx C	T/R	90% CI
C_{max} (ng/mL)	519 ± 129.1	575 ± 128.4	111	100 – 121
ln C_{max}	503	562	**112**	**101 – 124**
T_{max} (hr)	2.50 (1.00 – 4.00)	3.50 (1.50 – 4.00)	119	--
C_{min} (ng/mL)	49.9 ± 26.48	48.2 ± 16.27	96.7	76.3 – 117
AUC $_{0-t}$ (ng*hr/mL)	2809 ± 655.0	3127 ± 602.6	111	103 – 120
ln AUC $_{0-t}$	2735	3069	**112**	**103 – 123**
K_e (hr^{-1})	0.2639 ± 0.03288	0.2737 ± 0.03802	104	--
$t_{1/2}$ (hr)	2.67 ± 0.372	2.58 ± 0.371	96.7	--

Mean ± SD; Median (range); **Bold** = equivalence comparison

Results of study **PNFP-038** showed several statistically "significant" interactions for the pioglitazone components (e.g., 16% and 13% reductions in unchanged pioglitazone C_{max} and AUC) – however, none would suggest clinical concern. The most striking trend, however, was related to the gender-by-treatment effect for the ranitidine component. Males tended to have a consistent 10% reduction in ranitidine AUC and C_{max}, and females had a greater than 10% increase in ranitidine AUC and C_{max} – after both AM and PM dosing periods. As with the results from the pioglitazone component, this finding is not likely to be of clinical concern.

The third, and last, study, **PNFP-040.1**, evaluated the steady-state PK of pioglitazone (unchanged, total, and metabolites III and IV) on the steady-state PK of nifedipine ER, and vice versa. Twenty-five (13 male & 12 female) healthy subjects were administered one 15 mg and one 30 mg pioglitazone HCl tablet orally once daily in the morning for 7 days (**Tx A**), one 30 mg nifedipine ER tablet once daily in the morning for 4 days (**Tx B**), and a combination of treatments A and B for 4 days (**Tx C_1**) or 7 days (**Tx C_2**) in one of two sequences: SEQ 1 = Tx A, Tx C_1, Tx B, or SEQ 2 = Tx B, Tx C_2, Tx A. There was no washout between periods 1 and 2, and a 10-day washout between the last dose of Period 2 and the first dose of Period 3. Results of study **PNFP-040.1** are presented in tables 16 through 21.

Table 16: Unchanged Pioglitazone: Pioglitazone Alone (Tx A) Vs. Pioglitazone plus Nifedipine (Tx C)

Parameter	Tx A	Tx C	T/R	90% CI
C_{max} (ng/mL)	171 ± 493.1	1797 ± 581.1	105	93.7 – 116
ln C_{max}	1651	1720	**104**	**92.5 – 117**
T_{max} (hr)	2.00 (1.00 – 4.00)	2.00 (1.00 – 4.00)	95.6	--
C_{min} (ng/mL)	177 ± 68.4	187 ± 87.3	106	98.3 – 114
AUC $_{0-t}$ (ng*hr/mL)	14159 ± 3993.1	15048 ± 4884.1	106	97.9 – 115
ln AUC $_{0-t}$	13640	14355	**105**	**96.9 – 114**
K_e (hr^{-1})	0.0827 ± 0.02592	0.0731 ± 0.02683	88.8	--
$t_{1/2}$ (hr)	9.70 ± 5.229	11.3 ± 5.62	115	--

Mean ± SD; Median (range); **Bold** = equivalence comparison

Table 17: Pioglitazone M-III Metabolite: Pioglitazone Alone (Tx A) Vs. Pioglitazone plus Nifedipine (Tx C)

Parameter	Tx A	Tx C	T/R	90% CI
C_{max} (ng/mL)	555 ± 186.8	556 ± 192.0	100	94.1 – 106
ln C_{max}	534	532	**99.6**	**94.0 – 106**
T_{max} (hr)	4.00 (2.00 – 10.00)	4.00 (1.00 – 24.00)	112	--
C_{min} (ng/mL)	374 ± 117.8	397 ± 135.0	106	102 – 110
AUC $_{0-t}$ (ng*hr/mL)	10190 ± 3063.8	10595 ± 3446.5	104	99.0 – 109
ln AUC $_{0-t}$	9868	10185	**103**	**98.2 – 108**
K_e (hr^{-1})	--	--	--	--
$t_{1/2}$ (hr)	--	--	--	--

Mean ± SD; Median (range); **Bold** = equivalence comparison

Table 18: Pioglitazone M-IV Metabolite: Pioglitazone Alone (Tx A) Vs. Pioglitazone plus Nifedipine (Tx C)

Parameter	Tx A	Tx C	T/R	90% CI
C_{max} (ng/mL)	1567 ± 282.9	1583 ± 339.9	101	95.3 – 17
ln C_{max}	1546	1553	**100**	**94.9 – 106**
T_{max} (hr)	10.0 (3.00 – 24.00)	8.00 (2.00 ± 10.00)	82.2	--
C_{min} (ng/mL)	1086 ± 240.6	1105 ± 283.7	102	96.6 – 107
AUC $_{0-t}$ (ng*hr/mL)	30069 ± 5708.9	30475 ± 6688.7	101	96.8 – 106
ln AUC $_{0-t}$	29588	29837	**101**	**96.2 – 106**
K_e (hr^{-1})	--	--	--	--
$t_{1/2}$ (hr)	--	--	--	--

Mean ± SD; Median (range); **Bold** = equivalence comparison

Table 19: Total Pioglitazone: Pioglitazone Alone (Tx A) Vs. Pioglitazone plus Nifedipine (Tx C)

Parameter	Tx A	Tx C	T/R	90% CI
C_{max} (ng/mL)	3584 ± 796.9	3644 ± 823.6	102	95.3 – 108
ln C_{max}	3510	3570	**102**	**95.0 – 109**
T_{max} (hr)	2.00 (1.00 – 4.00)	2.00 (1.00 – 6.00)	102	--
C_{min} (ng/mL)	1637 ± 375.1	1689 ± 456.3	103	98.6 – 108
AUC $_{0-t}$ (ng*hr/mL)	54417 ± 11357.9	56117 ± 13529.1	103	98.0 – 108
ln AUC $_{0-t}$	53400	54742	**103**	**97.4 – 108**
K_e (hr^{-1})	--	--	--	--
$t_{1/2}$ (hr)	--	--	--	--

Mean ± SD; Median (range); **Bold** = equivalence comparison

Table 20: Nifedipine (Males): Nifedipine Alone (Tx B) Vs. Nifedipine plus Pioglitazone (Tx C)

Parameter	Tx B	Tx C	T/R	90% CI
C_{max} (ng/mL)	24.2 ± 8.73	18.4 ± 7.34	75.9	57.1 – 94.8
ln C_{max}	22.7	17.0	**74.8**	**61.6 – 90.8**
T_{max} (hr)	7.00 (3.00 – 12.00)	6.00 (0.00 – 12.00)	93.3	--
C_{min} (ng/mL)	12.5 ± 4.51	11.2 ± 6.63	89.8	75.5 – 104
AUC $_{0-t}$ (ng*hr/mL)	360 ± 129.3	286 ± 120.9	79.5	68.1 – 90.9
ln AUC $_{0-t}$	340	266	**78.3**	**69.4 – 88.4**
K_e (hr^{-1})	--	--	--	--
$t_{1/2}$ (hr)	--	--	--	--

Mean ± SD; Median (range); **Bold** = equivalence comparison

Table 21: Nifedipine (Females): Nifedipine Alone (Tx B) Vs. Nifedipine plus Pioglitazone (Tx C)

Parameter	Tx B	Tx C	T/R	90% CI
C_{max} (ng/mL)	22.0 ± 7.17	21.0 ± 7.93	94.5	77.8 – 111
ln C_{max}	21.6	19.8	**91.6**	**76.3 – 110**
T_{max} (hr)	4.00 (0.00 – 24.00)	6.00 (0.00 – 24.00)	159	--
C_{min} (ng/mL)	14.6 ± 6.68	15.2 ± 6.49	104	93.2 – 115
AUC $_{0-t}$ (ng*hr/mL)	339 ± 100.6	343 ± 124.1	100	89.7 – 111
ln AUC $_{0-t}$	336	331	**98.4**	**87.9 – 110**
K_e (hr^{-1})	--	--	--	--
$t_{1/2}$ (hr)	--	--	--	--

Mean ± SD; Median (range); **Bold** = equivalence comparison

The PK parameters for unchanged pioglitazone, total pioglitazone, and the two pioglitazone metabolites were found to be similar for both treatments A and C. Point estimates (T/R) ratio fell on or about 100% and the 90% confidence limits were contained within the equivalence standards of 80% to 125%.

Conversely, the C_{max} and AUC values for nifedipine were different between treatments B and C – most notably for the male subjects, whereby C_{max} was decreased by 25% and AUC by 22%. This degree of apparent inhibition was not observed in the female subjects. However, the females did exhibit an 8% reduction in C_{max} values, with 90% confidence limits falling below the low-end boundary at 76.3%. The AUC was not different between treatments for the female subjects.

LABELING –
Note:

Clinical Pharmacology / Pharmacokinetics Section just after Special Populations. Additionally, the sections describing Oral Contraceptives and Cytochrome P450 should remain in the Precautions Section.

CLINICAL PHARMACOLOGY section, **Drug-Drug Interactions** subsection:

The following drugs were studied in healthy volunteers with a co-administration of ACTOS 45 mg once daily. Listed below are the results:

Fexofenadine HCl: Co-administration of ACTOS for 7 days with 60 mg fexofenadine administered orally twice daily resulted
fexofenadine pharmacokinetics.

Glipizide: Co-administration of ACTOS and 5 mg glipizide administered orally once daily for 7 days did not alter the steady-state pharmacokinetics of glipizide.

Digoxin: Co-administration of ACTOS with 0.25 mg digoxin administered orally once daily for 7 days did not alter the steady-state pharmacokinetics of digoxin.

Warfarin: Co-administration of ACTOS for 7 days with warfarin did not alter the steady-state pharmacokinetics of warfarin. ACTOS has no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy.

Metformin: Co-administration of a single dose of metformin (1000 mg) and ACTOS after 7 days of ACTOS did not alter the pharmacokinetics of the single dose of metformin.

Ranitidine HCl: Co-administration of ACTOS for 7 days with ranitidine administered orally twice daily for either 4 or 7 days resulted in

Nifedipine ER: Co-administration of ACTOS for 7 days with 30 mg nifedipine ER administered orally once daily for 4 days

Ketoconazole: Co-administration of ACTOS and ketoconazole (200 mg)

Midazolam: Administration of ACTOS for 15 days followed by a single 7.5 mg dose of midazolam syrup resulted in a 26% reduction in midazolam C_{max} and AUC.

Oral Contraceptives: See **PRECAUTIONS**

Cytochrome P450: See **PRECAUTIONS**

PRECAUTIONS section, **Drug Interactions** subsection:

Oral Contraceptives: Administration of another thiazolidinedione with an oral contraceptive containing ethinyl estradiol and norethindrone reduced the plasma concentrations of both hormones by approximately 30%, which could result in loss of contraception. The pharmacokinetics of co-administration of ACTOS and oral contraceptives have not been evaluated in patients receiving ACTOS and an oral contraceptive. Therefore, additional caution regarding contraception should be exercised in patients receiving ACTOS and an oral contraceptive.

The cytochrome P450 isoform CYP3A4 is partially responsible for the metabolism of pioglitazone. Specific formal pharmacokinetic interaction studies have not been conducted with ACTOS and other drugs metabolized by this enzyme such as: erythromycin, astemizole, cisapride, corticosteroids, cyclosporine, HMG-CoA reductase inhibitors, tacrolimus, triazolam, and trimetrexate, as well as inhibitory drugs such as ketoconazole and itraconazole. In vitro, ketoconazole appears to significantly inhibit the metabolism of pioglitazone (see CLINICAL PHARMACOLOGY, Metabolism). ~~Pending the availability of additional data, patients~~ Patients receiving ketoconazole concomitantly with ACTOS should be evaluated more frequently with respect to glycemic control.

Steven B. Johnson, B.S.Pharm, Pharm.D.
Division of Pharmaceutical Evaluation-II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader:

FT initialed by Hae-Young Ahn, Ph.D., Team Leader:

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Steve Johnson
12/18/01 10:10:01 AM
BIOPHARMACEUTICS

Hae-Young Ahn
12/19/01 10:11:06 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-073/ S-010

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-073

Takeda Global Research & Development Center, Inc.
Attention: Mary Jo Pritza, MPH, PharmD
Manager, Regulatory Affairs
475 Half Day Road
Lincolnshire, IL 60069

Dear Dr. Pritza:

We refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Actos (pioglitazone hydrochloride) Tablets.

We have received the following submissions reporting on postmarketing study commitments:

Submission date	Application Number	Study Number	Commitment Number
Mar. 15, 2002	NDA 21-073/S-017	PNFP-344	1
Jan. 29, 2001	IND 33,729 (S/N 334)	PNFP-345	2
June 16, 2004	NDA 21-073/S-023	01-TL-OPI-504	7

1. Commitment Number 1
Commitment Description: Conduct an evaluation of the pharmacokinetic impact of concomitant administration of Actos and ketoconazole. This will be a two-way crossover study utilizing a single dose Actos and a single dose of ketoconazole. The protocol will be submitted to the FDA by September 30, 1999; the clinical investigation will begin no later than December 31, 1999, and the final study report will be submitted to the FDA by September 30, 2000.

2. Commitment Number 2
Commitment Description: Conduct a two-way, cross-over enzyme induction study in patients treated with pioglitazone hydrochloride and Midazolam hydrochloride. This will be a steady-state pharmacokinetic study with 2 weeks of Actos administration, and a single dose of midazolam HCl. The protocol will be submitted to the FDA by September 30, 1999; the clinical investigation will begin no later than December 31, 1999; and the final study report will be submitted to the FDA by September 30, 2000.

3. Commitment Number 7
Commitment Description: Conduct a randomized, placebo-controlled 6 month clinical study in patients with Type 2 diabetes and NYHA Class 2 and early Class 3 congestive heart failure.

Evaluation of safety and efficacy parameters will focus on hematologic and cardiac structure and function (echocardiographic or similar evaluation). A draft protocol will be submitted to the Agency by October 31, 1999. The study will be initiated within three months of final protocol agreement, but not later than April 15, 2000.

We have reviewed your submissions and conclude that the above commitments were fulfilled and the information from those studies was incorporated in the supplements listed below.

Commitment 1 - Supplement-017 approved January 17, 2003
Commitment 2 - Supplement-010 approved July 12, 2002
Commitment 7 - Supplement-023 approved August 3, 2004

The following commitment acknowledged in our July 15, 1999, letter is open:

1. Commitment Number 6
Commitment Description: Conduct a 3 year outcome study evaluating the occurrence of serious liver disease in 1000 patients treated with Actos compared to an appropriate control group. A draft protocol will be submitted to the Agency by October 31, 1999. The study will be initiated within three months of final protocol agreement, but not later than July 1, 2000.
Status: Study # 01-00-TL-OPI-506 is ongoing.

If you have any questions, call Jena Weber, Regulatory Project Manager, at 301-827-6422.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Enid Galliers
2/14/05 06:43:42 PM
Signing for Dr. Orloff

Division of Metabolic and Endocrine Drug Products

PROJECT MANAGER REVIEW

Application Number: NDA 21-073/S-010

Name of Drug: Actos (pioglitazone HCl) Tablets

Sponsor: Takeda Pharmaceuticals North America, Inc.

Material Reviewed: Package Insert

Submission Date: March 2, 2001

Receipt Date: March 5, 2001

Background and Summary:

Background and Summary Description: Actos Tablets are indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. It is indicated both as monotherapy, and in combination with a sulfonylurea, metformin or insulin when diet and exercise plus the single agent do not result in adequate glycemic control.

Supplement 010, provided for changes to the **PRECAUTIONS** section, **Drug Interactions** subsection. The pharmacokinetics of concomitant use of pioglitazone with the following compounds was added: fexofenadine, ranitidine, and nifedipine ER. The balance of the subsection was reworded to reduce redundancy.

Review: The DRAFT labeling from this submission (Identifier DN 2006, Revised March 2001), was compared to the currently approved package insert, approved on July 15, 2001, for supplement 011, Identifier 5012100 03 (revised May 2001). No other changes were made other than those specified by the sponsor. According to the December 19, 2001, review, Biopharm Reviewer and Team Leader (Drs. Steven Johnson and Hae-Young Ahn, respectively), [redacted] **CLINICAL PHARMACOLOGY** section, **Drug-Drug** Interactions subsection, to appear after **Ethnicity** in **Special Populations** subsection. The Oral Contraceptives subsection should remain under the **PRECAUTIONS** section, **Drug Interactions** subsection. [redacted] should also remain in the **PRECAUTIONS** section, **Drug Interactions** subsection. The verbiage however, remains unchanged from the previously approved package insert (supplement 011).

Conclusions: **Approvable** letter to issue, pending revised labeling which incorporates the above revisions.

Drafted: Jweber 12/18/01
Revised/Initialed:Kjohnson 1/3/02
Finalized:Jweber 1/3/02
Filename: ActosS-010

CSO LABELING REVIEW

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jena Weber
1/3/02 01:36:30 PM
CSO

Jena Weber
1/3/02 01:48:14 PM
CSO

EXCLUSIVITY SUMMARY for NDA # 21-073 SUPPL # 010

Trade Name Actos Generic Name Pioglitazone HCl

Applicant Name Takeda HFD-510

Approval Date January 3, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_X_/

   b) Is it an effectiveness supplement? YES /_X_/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE-8

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /_X_/ NO /___/

If yes, NDA # 21-073 Drug Name Actos

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain:

Investigation #2

IND # _____ YES /___/ NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

Jena M. Weber
Project Manager

January 3, 2002

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/s/

Jena Weber
1/3/02 02:03:39 PM

Memo to File

July 12, 2002

From: Hae-Young Ahn, Ph.D.

To: NDA 21-073/SE8-10

The proposed package insert for ACTOS faxed to the Agency on July 11, 2002 is acceptable.

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/s/

Hae-Young Ahn
7/12/02 09:56:26 AM
BIOPHARMACEUTICS

Division of Metabolic and Endocrine Drug Products

PROJECT MANAGER LABELING REVIEW (FA)

Application Number: 21-073/S-010 Actos (pioglitazone HCl) Tablets 15 mg, 30 mg, and 45 mg.
Sponsor: Takeda Inc.

Material Reviewed: Package insert (PI), final printed labeling.

Submission Date: August 30, 2002.

Background and Summary Description: Background and Summary Description: Actos Tablets are indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. It is indicated both as monotherapy, and in combination with a sulfonylurea, metformin or insulin when diet and exercise plus the single agent do not result in adequate glycemic control. NDA 21-073 was approved on July 15, 1999. Supplement 010, provided for changes to the **PRECAUTIONS** section, **Drug Interactions** subsection, and **CLINICAL PHARMACOLOGY** section, and was approved on July 12, 2002.

Review: The FPL for NDA 21-073/S-010 (Identifier 5012100-05, revised July 2002), was compared to the draft labeling approved with supplement 010 (Identifier DN 2006, revised March 2001). No changes were noted or indicated.

Conclusions: Issue A&R letter.

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/s/

Jena Weber
12/23/02 01:50:37 PM
CSO

Jena Weber
12/23/02 01:53:21 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-073/S-010

Takeda Pharmaceuticals North America, Inc.
Attention: Janet Haskins
Regulatory Affairs Supervisor
475 Half Day Road, Suite 500
Lincolnshire, Il 60069

Dear Ms. Haskins:

We acknowledge receipt of your August 30, 2002, submission containing final printed labeling in response to our July 12, 2002, letter approving your supplemental new drug application for Actos® (pioglitazone HCl) Tablets, 15 mg, 30 mg and 45 mg.

We have reviewed the labeling that you submitted in accordance with our July 12, 2002 letter and we find it acceptable.

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at 301-827-6422.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

David Orloff
12/23/02 04:10:48 PM

NDA 21-073/S-010

PRIOR APPROVAL SUPPLEMENT

Takeda Pharmaceuticals, North America, Inc.
Attention: Janet L. Haskins
Regulatory Affairs Supervisor
475 Half Day Road, Suite 500
Lincolnshire, IL 60069

Dear Ms. Haskins:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Actos® (pioglitazone) Tablets, 15 mg, 30 mg and 45 mg.

NDA Number: 21-073

Supplement Number: S-010

Review Priority Classification: Standard (S)

Date of Supplement: March 2, 2001

Date of Receipt: March 5, 2001

This supplement provides documentation in support of a package insert labeling change.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 4, 2001, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be January 5, 2002, and the secondary user fee goal date will be March 5, 2002.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at (301) 827-6422.

Sincerely,

{See appended electronic signature page}

Jena Weber
Regulatory Health Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

/s/

Jena Weber
4/3/01 11:35:22 AM